Trends in cardiovascular drug prescribing in Dutch general practice:

role of patient and physician related characteristics

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The studies presented in this thesis were supported by an unconditional grant from the Dutch Health Care Insurance Board and University of Groningen, the Netherlands.

Financial support by the Netherlands Heart Foundation, Dutch Diabetes Research Foundation, and University of Groningen for the publication of this thesis is gratefully acknowledged.

Additional support for printing of this thesis was received from the Northern Centre for Healthcare Research (NCH), Groningen University Institute for Drug Exploration (GUIDE), AstraZeneca BV, Boehringer Ingelheim BV, and Merck Sharp & Dohme BV.

Greving, JP
Trends in cardiovascular drug prescribing in Dutch general practice: role of patient and physician related characteristics
Dissertation University of Groningen, The Netherlands – with a summary in Dutch

ISBN: 90-77113-53-3

Printed by: Gildeprint BV, Enschede, the Netherlands
Cover design: Frank Holtkamp

RIJKSUNIVERSITEIT GRONINGEN

Trends in cardiovascular drug prescribing in Dutch general practice:

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Proefschrift

ter verkrijging van het doctoraat in de
Medische Wetenschappen
aan de Rijksuniversiteit Groningen
op gezag van de
Rector Magnificus, dr. F. Zwarts,
in het openbaar te verdedigen op
woensdag 10 januari 2007
om 14.45 uur

door
Jacoba Petronella Greving
geboren op 15 maart 1977
te Groningen

Promotores:
Prof. dr. F.M. Haaijer-Ruskamp
Prof. dr. D. de Zeeuw

Copromotor:
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Voor mijn ouders

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Chapter 1

General Introduction

Cardiovascular disease (CVD) is the leading cause of death in most industrialised countries. In 2004, approximately 45.000 persons died from cardiovascular disease in The Netherlands. Cardiovascular disease accounts for 33% of all deaths in both men and women.[1] Therefore, efforts to optimise preventive therapy are warranted.
Hypertension and hyperlipidemia are the two most common risk factors for CVD that can be modified with lifestyle interventions and pharmacotherapy. Although the efficacy and safety of antihypertensive and lipid-lowering drugs have been extensively established in clinical trials, they appear not to be used to their full benefit in daily medical practice.

Drug prescribing in daily medical practice

Cardiovascular drugs should be targeted to the appropriate patients, and both undertreatment and overtreatment may occur.[2] Undertreatment can be defined as inappropriately not receiving medication but also includes uncontrolled disease status despite pharmacological treatment. Undertreatment in high risk patients is common in cardiovascular medicine.[3-6] Conversely, overtreatment may occur when guidelines restrict drug use to certain subpopulations while drugs are prescribed to a non-selective group of patients or newer agents are used with no proven benefit over other effective and longer available drugs. This appeared to have happened with regard to the newer classes of antihypertensives.[7-10] Undertreatment should be prevented in order to gain optimal benefit in those most in need of therapy, whereas overtreatment should be avoided to limit unnecessary health risk and spending of health care resources.

To improve antihypertensive and lipid-lowering drug prescribing, insight in the patterns and determinants related to cardiovascular drug prescribing on the level of the individual patient and the physician is needed.

Evidence and guideline recommendations related to cardiovascular drug prescribing

The quality of drug prescribing is often assessed from an evidence-based medicine point of view. In the past decade, increasing attention has been paid to evidence-based medicine, and many guidelines have been developed based on systematically obtained, best available evidence. In the Netherlands, the Dutch College of General Practitioners and Dutch Institute for Healthcare Improvement (CBO) regularly publish and update national guidelines. These guidelines are designed to help physicians in making decisions about the care of individual patients.
In most of these guidelines, recommendations are given regarding screening, diagnosis, treatment and first-choice drugs. Therefore, they can serve as the ‘gold standard’ when

assessing the quality of pharmacotherapy in daily medical practice. This section will provide a short overview of the evidence and guideline recommendations for hypertension and hyperlipidemia management.

Efficacy of antihypertensive and lipid-lowering drugs

The benefits of antihypertensive and lipid-lowering therapy for the prevention of cardiovascular disease are well-known.[11-13] The early studies documenting the beneficial effects of treatment of hypertension were carried out using diuretics or beta-blockers. Over the past two decades, it has been shown that drugs from newer classes also reduce major cardiovascular events. This is the case for angiotensin-converting enzyme (ACE) inhibitors and, more recently, the angiotensin II receptor blockers (ARBs).[14-17] Moreover, these drugs have renoprotective effects beyond those resulting from lowering blood pressure alone.[18-22] With regard to lipid-lowering therapy, the HMG-CoA reductase inhibitors (statins) have proven to be effective in reducing cardiovascular morbidity and mortality across a broad range of patient groups.[23-27]

Guidelines for hypertension management

In the period 1996-2005, the Dutch College of General Practitioners released updates of their practice guideline on hypertension in 1997, 1999, and 2003.[28-30] In addition, a new consensus guideline on hypertension was released by the Dutch Institute for Health Care Improvement (CBO) in 2000.[31] In all guidelines, diuretics and beta-blockers remained the drugs of first choice in patients with uncomplicated hypertension. ACE inhibitors and calcium channel blockers may be added when the blood pressure remains too high. ACE inhibitors were recommended as first-choice drugs in all hypertensive patients with diabetes in the Dutch consensus guideline from 2000, while in the practice guidelines from the Dutch College of General Practitioners ACE inhibitors were only suggested for patients with diabetes and microalbuminuria. ACE inhibitors in combination with diuretics were recommended in hypertensive patients with heart failure in all guidelines. ARBs were first mentioned in the Dutch consensus guideline on hypertension from 2000, as alternative for patients who do not tolerate ACE inhibitors. Between 1997 and 2003, the threshold values for the diagnosis hypertension in the guidelines were lowered from 160/95 mmHg to 140/90 mmHg.

Guidelines for hyperlipidemia management

A revised consensus guideline on the management of hyperlipidemia by the Dutch Institute for Healthcare Improvement (CBO) was released in 1998, after the publication of the first landmark trials on the efficacy of statins.[32] In 1999, the Dutch College of General Practitioners launched their own guideline, which differed only marginally from the consensus guideline.[33] Both guidelines indicate lipid-lowering therapy for the primary prevention of CVD to patients at high risk for CVD: i.e. patients with a history of cardiovascular disease, patients with a

(suspected) hereditary lipid disorder or patients with a 10-year coronary heart disease (CHD) risk larger than 25%. To eliminate the need to calculate this risk, the guidelines incorporate risk tables that indicate the predicted CHD risk using six risk factors: age, cholesterol (as total cholesterol/HDL ratio), blood pressure, smoking, diabetes, and gender.

Patterns of cardiovascular drug prescribing and patient-related factors

Given the changes in recommendations regarding antihypertensive treatment, one might expect an overall increase in the use of antihypertensives in the past decade, whereas increases in the use of newer classes of antihypertensives are more likely in the specific patient groups for which they have been recommended. In other words, according to the recommendations increases in the use of ACE inhibitors and ARBs should have been largest in hypertensive patients who also have heart failure or diabetes mellitus, especially in the presence of microalbuminuria. To get better insight into the quality of antihypertensive treatment and potential overtreatment with newer agents, it is therefore important to investigate trends in prescribing of ACE inhibitors and ARBs as initial and second-line treatment for hypertension, and to clarify the role of comorbidity in explaining these trends.

Treatment decisions with regard to hyperlipidemia should be based on a combined assessment of multiple cardiovascular risk factors to target prevention to patients at high cardiovascular risk. There are doubts, however, that such a high-risk approach in the primary prevention of cardiovascular disease has been implemented in daily medical practice.[34;35] Insight into whether patients with both elevated blood pressure and elevated lipid levels were more likely to receive lipid-lowering therapy, can help us to guide future efforts to improve the quality of lipid-lowering drug prescribing.

Physician factors related to cardiovascular drug prescribing

Much research has focused on the relation between physician characteristics and drug prescribing. General physician characteristics, such as age, gender or year of graduation, are sometimes found to be associated with specific prescribing patterns but these findings are not consistent.[36-38] Moreover, these characteristics cannot be modified. Others have looked at internal factors related to the prescribing process, such as knowledge, attitudes and personal experience of the prescriber, showing that treatment choices are not always the result of carefully reasoned decision making.[39-41] External factors, such as commercial information sources and the professional network, may influence drug choice and adoption of new drugs.[42]

This section will address some issues related to these external factors relevant for understanding the dynamics of (new) drug prescribing.

Influences of professional and commercial information sources

The literature pertaining to the prescribing of new drugs by general practitioners clearly identified commercial information sources as one of the key influences on their adoption of new drugs.[43-46] Over the past decade, however, there has been a growing emphasis on practicing evidence-based medicine in drug prescribing. This raises the question whether professional information sources currently counterbalance the influence of commercial information sources in the adoption process.

Pharmaceutical drug advertising in medical journals

In step with the growing popularity of evidence-based medicine, the pharmaceutical industry is incorporating clinical trial results and bibliographic references in drug advertisements more frequently than previously.[47-49] Use of clinical trials is especially evident in promotion of antihypertensive and lipid-lowering drugs, as a way for pharmaceutical companies to succeed in an environment marked by intense competition between a host of similar drugs in the same therapeutic group.[50] In fact, the use of clinical trials is now an important marketing strategy. Pharmaceutical companies use randomised clinical trials to obtain results on safety and efficacy on hard endpoints to distinguish their product from its competitors and to improve their product's position in the market.[48;51] The newest antihypertensive drug class, the ARBs, forms an interesting case to study how new research findings are presented in drug advertisements over time.

Specialists' attitudes towards treatment guidelines

An important issue for drug choices in chronic diseases forms the interaction between general practitioners and hospital physicians. Hospital physicians can have a great impact on treatment at the general practitioners level. Nevertheless, they are often not included in efforts to improve treatment in primary care. In the year 2000, a program was set up in the Netherlands to improve the quality of treatment care across the primary-secondary care interface. The aim was to improve both quality and efficiency in health care by bringing the therapeutic care provided by general practitioners and specialists in line with each other. In some regions, joint treatment guidelines were developed recommending specific drug choices for a range of diseases. Previous research showed that hospital physicians expressed mixed attitudes towards such joint treatment guidelines, and their willingness to follow the recommendations seemed low.[52;53] One might expect that the attitudes differ between hospital settings because of differences in organisational culture and patient populations.[54-56] Better insight in differences in attitudes across hospital settings is needed to find ways to promote the use of joint treatment guidelines.

Aims and outline of this thesis

The main objective of this thesis is to explore trends in cardiovascular drug prescribing, and to assess whether antihypertensive drugs, in particular ACE inhibitors and ARBs, and lipid-lowering drugs were prescribed appropriately and according to the guideline recommendations in Dutch general practice. The studies in this thesis will show whether patient-related factors influence antihypertensive and lipid-lowering drug prescribing, and will give insight into factors which influence the general practitioners' decision to prescribe (new) drugs.

The first part of this thesis consists of three studies focusing on patterns of antihypertensive and lipid-lowering drug prescribing and the influence of patient-related factors. **Chapter 2** presents trends in prevalent and initial use of ACE inhibitors and ARBs in the treatment of hypertension, and clarifies the role of comorbidity. **Chapter 3** emphasizes on prescribing of ARBs as initial and second-line therapy. **Chapter 4** describes trends in initiating and intensifying antihypertensive and lipid-lowering therapy in type 2 diabetes patients and examines predictors of these treatment changes.

The second part of this thesis describes physician-related factors associated with prescribing (new) drugs. **Chapter 5** describes which physician-related factors are associated with early adoption of ARBs. **Chapter 6** evaluates how the pharmaceutical industry deals with this evolving clinical evidence in their advertising claims for the different ARBs. **Chapter 7** addresses specialists' attitudes towards cardiovascular treatment guidelines for primary and secondary care.

Finally, in **chapter 8** the main findings and conclusions are discussed and put into a general perspective for further improvement of cardiovascular drug prescribing.

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Part I

Patterns of cardiovascular drug prescribing and patient-related factors

Chapter 2

Does comorbidity explain trends in prescribing of newer antihypertensive agents?

Jacoba P Greving, Petra Denig, Willem Jan van der Veen, Frank W Beltman, Miriam CJM Sturkenboom, Dick de Zeeuw, and Flora M Haaijer-Ruskamp
Journal of Hypertension 2004; 22: 2209-2215

Abstract

Objective

Concerns exist about heavily prescribing of new drugs when the evidence on hard outcomes is still limited. This has been the case for the newer classes of antihypertensives, especially in hypertensive patients without additional comorbidity. The association between comorbidity and trends in prescribing of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) was examined for the period 1996-2000.

Design and methods

Data were obtained from the Integrated Primary Care Information database, which contains medical records from more than 100 general practitioners in the Netherlands. Prevalent drug use in hypertensive patients was determined per calendar year. As initial treatment, the first antihypertensive drug prescribed within 1 year after diagnosis of hypertension was considered. Logistic regression was used to estimate the likelihood of receiving either ACE-I or ARBs.

Results

The overall prevalent ACE-I use remained stable (31%), but it increased from 33% to 41% in hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency. ARB use increased significantly from 2% to 12%; this trend did not differ between patients with or without specific comorbidities. Initial ACE-I use slightly decreased (from 29% to 24%), while initial ARB use significantly increased (from 4% to 12%). ACE-I were more likely to be the first treatment in patients with diabetes [odds ratio (OR) = 3.9; 95% confidence interval (CI) 3.2-4.9] or hypercholesterolemia (OR=1.4;1.1-1.8). ARBs were more likely to be the initial treatment in patients with asthma/chronic obstructive pulmonary disease (OR=1.6;1.2-2.3), diabetes (OR=2.1;1.5-2.9) or hypercholesterolemia (OR=1.7;1.2-2.4).

Conclusions

The increased use of ACE-I is mostly restricted to hypertensive patients with comorbidities for which their use has been recommended. Trends in prescribing of ARBs are not related to relevant comorbidities.

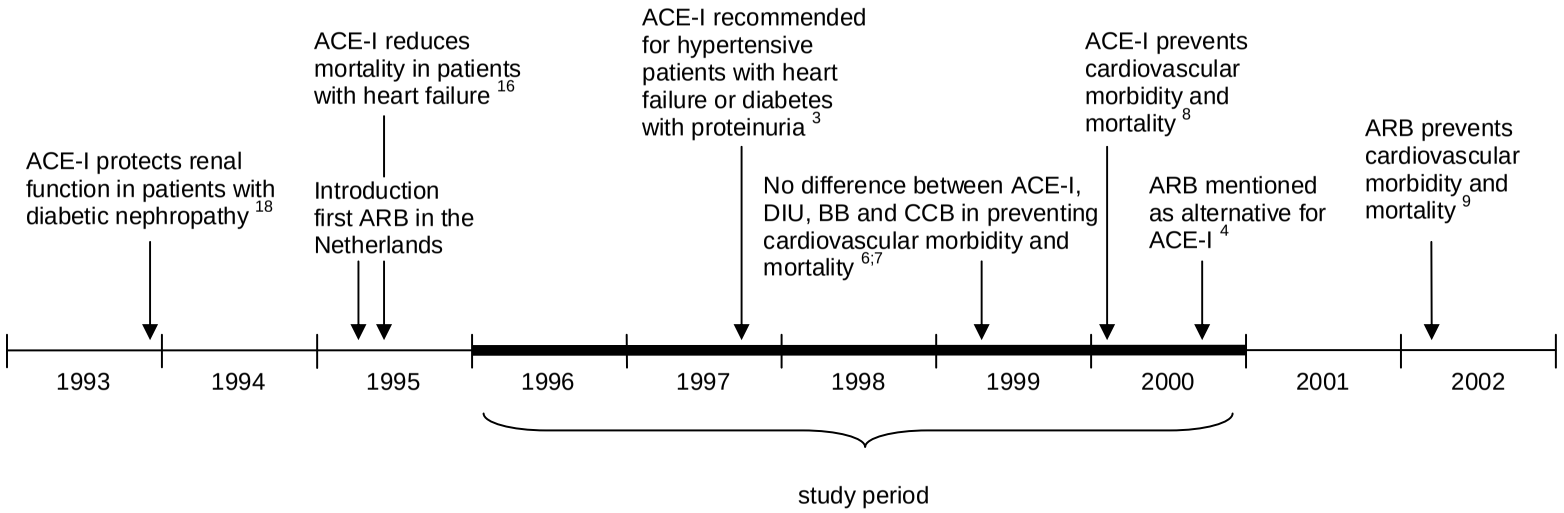
Introduction

There is an ongoing debate regarding which drug class should be preferred for treating hypertension.[1;2] Over the years, most national and international guidelines have recommended diuretics and beta-blockers as first-choice agents for the treatment of hypertension without comorbidity because benefits on hard outcomes have been demonstrated for these drugs.[3-5] One of the debated issues is the role that angiotensin-converting enzyme inhibitors (ACE-I) and, more recently, angiotensin II receptor blockers (ARBs) have in treating uncomplicated hypertension. The first studies showing benefits in terms of cardiovascular morbidity and mortality in hypertension patients were published in 1999 for ACE-I [6-8], and in 2002 for ARBs [9] (**Figure 1**). However, during the preceding years in which the cardiovascular disease outcomes of these newer antihypertensive drugs were largely unknown, large shifts were observed in the use of these drugs in hypertensive patients.[10-15]

However, evidence that ACE-I are effective in reducing morbidity and mortality in patients with heart failure or diabetes mellitus was available several years earlier.[16-18] Based on this evidence, ACE-I have been recommended in the Dutch hypertension guidelines since 1997 as first-choice agents for hypertensive patients who also have heart failure or diabetes mellitus, especially in the presence of proteinuria.[3;4] ARBs, which were introduced in The Netherlands in 1995, were first mentioned in a Dutch hypertension guideline in 2000, and are recommended as alternative for ACE-I when these drugs are not well tolerated.[4] It might be expected that increases in the use of ACE-I and ARBs have been the largest in these specific patient groups for which they have been recommended. In a survey conducted in the USA in 1997, primary care physicians reported that they increased the use of ACE-I as initial therapy for hypertensive patients with heart failure or diabetes.[19] Cross-sectional analyses of prescription data showed that ACE-I were more likely to be prescribed in hypertensive patients with certain comorbidities, such as diabetes, hypercholesterolemia, heart failure, history of myocardial infarction or angina pectoris.[11-13] There are also some descriptive studies indicating that the increased ACE-I use is influenced by the presence of comorbidities, such as diabetes.[20;21] However, these studies do not rigorously analyse the effect of comorbidity on changes in ACE-I and ARB prescribing over time. Given the difference in available evidence and recommendations on hard outcomes, it is important to analyse trends in the prescribing of ARBs separate from ACE-I.

The aim of this study was to examine the trends in prevalent and initial use of ACE-I and ARBs in comparison with other drug classes for the treatment of hypertension from 1996 to 2000, and to clarify the role of comorbidity in explaining these trends. The findings will shed new light regarding the extent that physicians anticipate on or follow the available scientific evidence and guideline recommendations.

Figure 1 Relevant trial results and Dutch guideline recommendations regarding ACE inhibitors and angiotensin II receptor blockers before, during and after the study period



ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DIU, diuretic; BB, beta-blocker; CCB, calcium channel blocker

Methods

Setting

In this study, data from the Integrated Primary Care Information (IPCI) database from the Erasmus Medical Center were used. This is a longitudinal general practice research database containing the complete electronic medical records from more than 100 Dutch general practitioners (GPs) participating on a voluntary basis, receiving a yearly financial reward. In The Netherlands, patients are registered to a single GP who has a gatekeeper role in coordinating their medical care. GPs contributing to the IPCI database are not permitted to use paper-based records in addition to their electronic medical records. They all prescribe electronically using a uniform coding system, and use the International Classification for Primary Care (ICPC) for diagnosis coding.[22] Information on drug prescriptions comprises brand name, quantity, strength, indication, prescribed daily dose and the anatomical therapeutical chemical classification (ATC) code.[23] The computer records further contain information on patient demographics, referrals, and textual medical data entered by the GP. Thus, the records can be considered to contain all drug prescriptions, and all clinical information considered relevant by the GPs for providing adequate care for their patients. The database complies with European Union guidelines on the use of medical data for medical research, and has been proven valid using different reference methods for pharmaco-epidemiological research.[24]

Study period and population

The 5-year study period started on 1 January 1996 and ended on 31 December 2000. The source population comprised all individuals aged more than 18 years who had at least 6 months registration with their GP in the IPCI database during the study period. All patients with either a ICPC-coded diagnosis of hypertension or hypertension in the patient diary as free text were selected. This latter group was manually evaluated to include only those patients where hypertension was mentioned as their diagnosis.

For hypertensive patients, all prescriptions written after diagnoses of hypertension for any of the five main antihypertensive drug classes were selected. This includes diuretics, beta-blockers, calcium channel blockers, ACE-I and ARBs. Furthermore, for each patient, the presence of specific comorbidities using the ICPC-codes and free text or, when possible, the ATC-code for indication-specific drugs were identified. The following comorbidities that might influence the choice of hypertension treatment were included: angina pectoris, ankle oedema, arrhythmia, asthma and/or chronic obstructive pulmonary disease (COPD), diabetes mellitus, gout, heart failure, hypercholesterolemia, myocardial infarction, proteinuria and/or renal insufficiency, and stroke. Data were also collected on referrals to an internist or cardiologist because patients with comorbidities are more likely to be referred to a specialist, and specialists have been found to prescribe more ACE-I than GPs.[25]

Estimation of antihypertensive drug use

To be able to look at trends in use of antihypertensives in independent groups of patients, 20% of all patients registered in the IPCI database in each calendar year were randomly sampled. For each calendar year, prevalent antihypertensive drug use was estimated on the first Wednesday in October. A hypertensive patient was defined as prevalent user of a certain class of antihypertensive drugs based on the last prescription in the 6 months before the index date. Initial drug use was assessed for all newly diagnosed hypertensive patients as the first antihypertensive drug prescribed within 1 year after the diagnosis, excluding patients who used any antihypertensive drugs in the 6 months before initiation of hypertension therapy.

Statistical analyses

The outcome variables studied were prevalent and initial use of ACE-I and ARBs, including monotherapy as well as combination therapy containing an ACE-I or ARB. The likelihood of receiving ACE-I or ARB was estimated through logistic regression analysis. As a reference category, users of classic antihypertensives (i.e. diuretics, beta-blockers, and calcium channel blockers) were chosen. In all models, an adjustment was made for sex and age (categorized as 18-50, 50-59, 60-69, 70-79, 80 years and above), because substantial sex and age differences have been found in antihypertensive drug choice.[11] First, the effect of comorbidity or referrals to a cardiologist or internist were explored in separate univariate models, that included also year, sex and age. To verify whether a specific comorbidity explained the time trend in the likelihood of receiving an ACE-I or ARB, an interaction term consisting of the comorbidity in question and calendar year was added in each univariate regression model. If this interaction term was significant and the stratified analysis showed a trend over the years than this comorbidity would partly explain trends in prescribing of newer antihypertensives. Next, all significant factors were included in the final multivariate logistic regression model using a stepwise procedure.

Results

The number of individuals aged more than 18 years who were registered for at least 6 months in the IPCI database increased from 95.974 in 1996 to 160.397 in 2000. In our random samples in each calendar year, a total of 115.344 patients were selected and 10.706 patients with a diagnosis of hypertension were identified. Hypertensive patients had a mean ± SD age of 63 ± 14 years, and 61% were women (ranging from 54% in the lowest age group to 77% in the highest age group). Of these patients, 54% had hypertension with at least one comorbidity; 1.774 (17%) had diabetes, 1.835 (17%) had hypercholesterolemia, and 553 (5.2%) had heart failure. The average number of comorbidities increased from 0.4 in the lowest age group to 1.4 in the highest age group.

Prevalent antihypertensive drug use

In the 10.706 patients with a hypertension diagnosis, 7.550 hypertensive patients who were prevalent users of any antihypertensive drug were identified. From 1996 to 2000, prevalent antihypertensive drug use varied from 68% to 73% in all hypertensive patients. Prevalent use of the five antihypertensive drug classes differed between various patient subgroups (e.g. sex, age, referrals, and comorbidities) (**Table 1**).

Table 1 Prevalent use of diuretics, beta-blockers, calcium channel blockers, ACE inhibitors (ACE-I) or angiotensin II receptor blockers (ARBs) in 7.550 treated hypertensive patients.

	n (%)	% Diuretics	% Beta-blockers	% CCB	% ACE-I	% ARBs
Period of time						
1996	1.044 (14)	41.0	38.2	22.1	31.8	2.1
1997	1.499 (20)	42.3	41.3	20.1	30.8	3.8
1998	1.786 (24)	41.6	41.7	21.1	31.2	7.4
1999	1.903 (25)	39.9	41.3	18.5	30.4	10.8
2000	1.318 (17)	41.3	42.9	20.6	31.6	11.5
Sex						
Male	2.776 (37)	31.7	41.0	24.3	36.7	8.2
Female	4.774 (63)	46.7	41.4	18.0	27.8	7.1
Age						
< 50 year	929 (12)	27.2	46.3	14.7	32.7	8.1
50-59 year	1.625 (22)	35.1	48.4	18.3	32.0	8.3
60-69 year	1.920 (25)	39.5	42.8	21.5	31.9	7.2
70-79 year	2.083 (28)	46.3	37.1	22.9	29.8	7.9
80 year and above	993 (13)	56.4	30.5	21.1	29.2	5.5
Referral						
Internist	1.784 (20)	40.8	36.2	26.0	34.3	9.1
Cardiologist	1.532 (24)	37.2	42.6	28.8	31.3	9.7
Comorbidity						
No comorbidity	3.306 (44)	40.7	46.0	15.4	28.5	7.4
Angina pectoris	878 (12)	37.4	47.3	32.5	26.4	7.2
Ankle oedema	691 (9)	57.3	30.8	22.9	25.6	7.5
Arrhythmia	691 (9)	41.1	38.8	23.7	31.1	9.4
Asthma / COPD	669 (9)	46.5	22.6	26.0	33.2	11.8
Diabetes	1.308 (17)	44.0	33.3	22.6	39.8	7.0
Gout	389 (5)	40.1	41.4	25.4	37.3	6.7
Heart failure	454 (6)	62.3	21.1	17.8	36.1	8.6
Hypercholesterolemia	1.344 (18)	35.0	43.1	26.9	34.3	8.8
Myocardial infarction	482 (6)	36.1	51.0	32.2	31.7	6.0
Proteinuria / renal insufficiency	185 (2)	44.3	31.9	28.6	37.3	11.4
Stroke	560 (7)	40.5	36.1	28.0	31.1	8.9

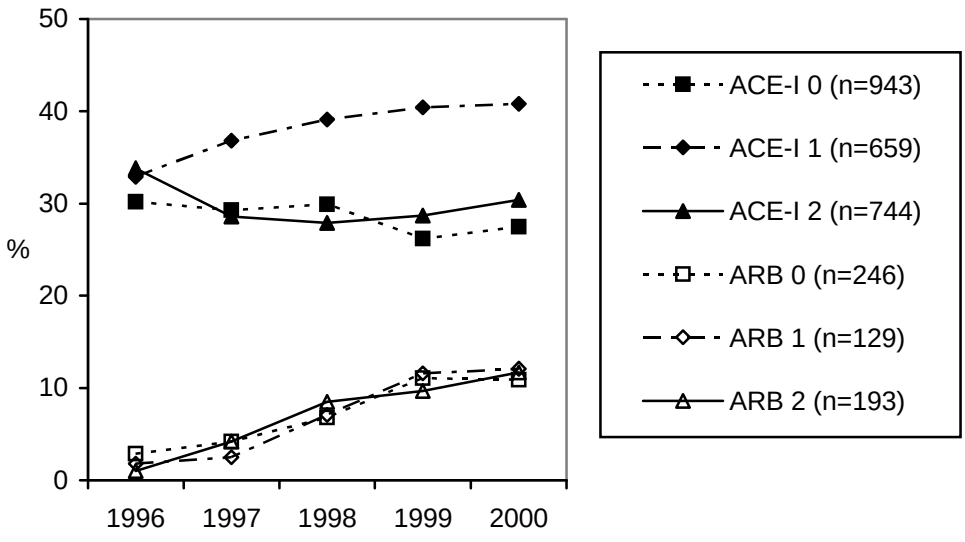
CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; COPD, chronic obstructive pulmonary disease.

Time trends showed that there was a significant increase in prevalent use of beta-blockers (from 38% to 43%) and ARBs (from 2% to 11%), whereas prevalent use of calcium channel blockers somewhat decreased (from 22% to 21%), and prevalent use of diuretics (41%) and ACE-I (31%) remained stable over the years. Overall, the average number of antihypertensives prescribed per patient increased from 1.4 to 1.5.

Prevalent ACE-I use

In hypertensive patients without any comorbidity, approximately 29% were treated with an ACE-I. In hypertensive patients who also suffered from diabetes, heart failure, proteinuria and/or renal insufficiency the prevalent use of ACE-I increased from 32.9% to 40.8% (**Figure 2**). The univariate analysis confirmed that diabetes, heart failure and proteinuria and/or renal insufficiency were the strongest predictors of ACE-I use [odds ratios (OR) 1.7, 1.4 and 1.4, respectively]. Other significant comorbidities were hypercholesterolemia (OR=1.2), angina pectoris (OR=0.8), and ankle oedema (OR=0.8). Multivariate logistic regression showed that ACE-I were significantly more likely to be prescribed than classic antihypertensives to patients with diabetes, heart failure, hypercholesterolemia, or patients referred to an internist (**Table 2**). Patients with angina pectoris or ankle oedema were less likely to be prescribed ACE-I. No significant interactions were detected between individual comorbidities and trends in prevalent use of ACE-I, although the interaction between diabetes and trends in prevalent ACE-I use was of borderline significance (test for interaction, $P = 0.058$).

Figure 2 Prevalent use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in 7.550 treated hypertensive patients grouped by comorbidity (group 0 = no comorbidity, group 1 = diabetes, heart failure, proteinuria and/or renal insufficiency, group 2 = other comorbidity)



In 2000, hypertensive patients with diabetes were more likely to be prescribed ACE-I than in 1996 [OR=1.8; 95% confidence interval (CI) 1.2-2.8]. When combining patients with at least one comorbidity for which ACE-I are recommended (i.e. diabetes, heart failure, proteinuria and/or renal insufficiency), a significant interaction between these comorbidities and trends in prevalent ACE-I use was found (test for interaction, *P* = 0.030). In 2000, hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency were more likely to be prescribed ACE-I than in 1996 (OR=1.7; 95% CI 1.1-2.6).

Table 2 Patient characteristics independently associated with prevalent use or initial use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in treated hypertensive patients

	ACE-I; OR (95% CI)		ARB; OR (95% CI)	
Characteristics	Prevalent use	Initial use	Prevalent use	Initial use
Year				
1996		Reference	Reference	Reference
1997	-	0.9 (0.7 - 1.2)	1.7 (1.1 - 2.9)	1.9 (1.1 - 3.2)
1998	-	0.8 (0.6 - 1.0)	3.8 (2.4 - 6.0)	2.3 (1.4 - 3.8)
1999	-	0.7 (0.5 - 0.9)	5.5 (3.5 - 8.7)	2.9 (1.8 - 4.6)
2000	-	0.8 (0.6 - 1.0)	6.0 (3.8 - 9.5)	3.1 (1.9 - 5.0)
Age				
< 50 year			Reference	
50-59 year	-	-	1.0 (0.7 - 1.3)	-
60-69 year	-	-	0.9 (0.6 - 1.2)	-
70-79 year	-	-	0.9 (0.7 - 1.2)	-
80 year and above	-	-	0.6 (0.4 - 0.9)	-
Sex				
Female	0.6 (0.6 - 0.7)	0.6 (0.6 - 0.8)	0.8 (0.6 - 0.9)	0.8 (0.6 - 1.0)
Referral				
Internist	1.2 (1.1 - 1.4)	1.3 (1.1 - 1.6)	1.3 (1.1 - 1.6)	-
Cardiologists	-	1.4 (1.1 - 1.7)	1.6 (1.2 - 2.0)	-
Comorbidity				
Angina pectoris	0.7 (0.6 - 0.8)	-	0.7 (0.5 - 1.0)	-
Ankle oedema	0.7 (0.6 - 0.9)	-	-	0.4 (0.2 - 0.8)
Asthma / COPD	-	-	1.8 (1.4 - 2.3)	1.6 (1.2 - 2.3)
Diabetes	1.6 (1.4 - 1.8)	3.9 (3.2 - 4.9)	-	2.1 (1.5 - 2.9)
Heart Failure	1.4 (1.1 - 1.7)	-	-	-
Hypercholesterolemia	1.2 (1.1 - 1.4)	1.4 (1.1 - 1.8)	-	1.7 (1.2 - 2.4)
Myocardial Infarction	-	-	0.6 (0.4 - 1.0)	-

COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval.

Initial ACE-I use

From 1996 to 2000, 3.973 newly treated hypertensive patients were identified. More than one-quarter of these patients were younger than 50 years of age and 40% had at least one comorbidity. The percentage of initial ACE-I use in newly treated hypertensive patients decreased from 28.7% to 23.5%. In hypertensive patients who also had diabetes, heart failure, proteinuria and/or renal insufficiency, the percentage starting on an ACE-I was much higher, and increased from 42.7% to 51.8% in 1998 but decreased again to 44.4% in 2000 (**Figure 3**). Multivariate logistic regression showed that ACE-I were more likely to be the initial therapy compared with classic antihypertensives for patients with diabetes or hypercholesterolemia (**Table 2**). No significant interaction between comorbidity and trends in initial use of ACE-I was found. However, initial ACE-I use and year tended to be related among hypertensive patients with diabetes (test for interaction, $P = 0.057$), and among hypertensive patients with at least one of the comorbidities diabetes, heart failure, proteinuria and/or renal insufficiency (test for interaction, $P = 0.060$).

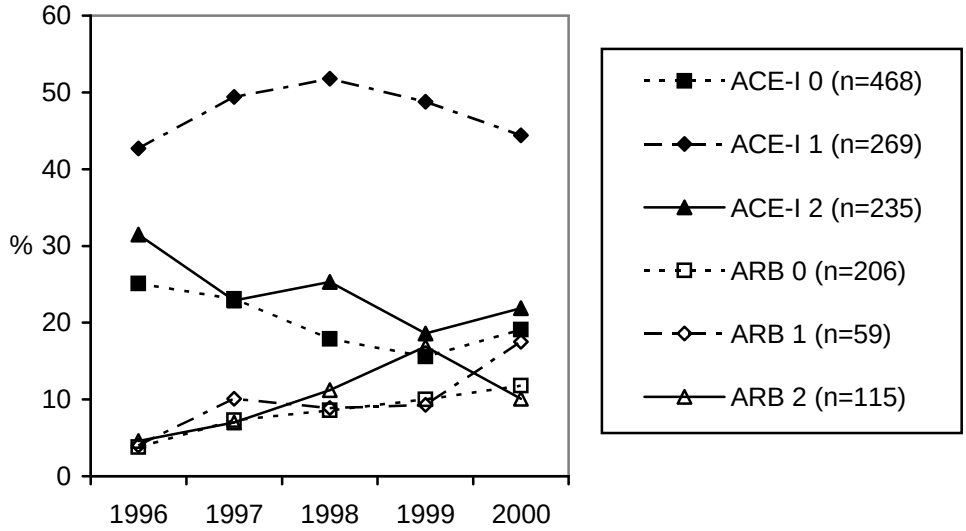
Prevalent ARB use

Trends in prevalent use of ARB did not differ between patients with or without comorbidities (**Figure 2**). In the univariate analysis, asthma and/or COPD, and proteinuria and/or renal insufficiency were the strongest predictors of ARB use (OR=1.8 and 1.8, respectively). Multivariate analysis showed that prevalent ARB use was more likely in patients with asthma and/or COPD and patients referred to a cardiologist or internist (**Table 2**). Patients with a history of myocardial infarction were less likely to be prescribed an ARB. No significant interactions were detected between individual comorbidities and trends in prevalent use of ARBs.

Initial ARB use

Initial ARB use increased significantly from 4.0% to 12.2%, mostly at the expense of initial ACE-I use (28.7% to 23.5%) and calcium channel blocker use (11.6% to 6.2%). Increases in initial ARB use did not differ between patients with or without comorbidities (**Figure 3**). ARBs were more likely to be initially prescribed to patients with diabetes, hypercholesterolemia, asthma and/or COPD than classic antihypertensives (**Table 2**). Patients with ankle oedema were less likely to be prescribed an ARB as initial therapy. We found no significant interaction between comorbidity and trends in initial use of ARBs.

Figure 3 Initial use of angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II receptor blockers (ARBs) in 3.973 newly treated hypertensive patients grouped by comorbidity (group 0 = no comorbidity, group 1 = diabetes, heart failure, proteinuria and/or renal insufficiency, group 2 = other comorbidity)



Discussion

This study showed significant trends in the choice of antihypertensive treatment in the period from 1996 to 2000, which correspond with the general trends in antihypertensive prescriptions in The Netherlands.[26] There is an increased use of antihypertensive drug treatment in general, and specific increases in the use of beta-blockers and ARBs. Although the overall use of ACE-I had stabilized, we observed an increased use of ACE-I in patients for which such drugs were recommended (i.e. hypertensive patients with diabetes, heart failure, proteinuria and/or renal insufficiency). ARB use increased significantly in all hypertensive patients, but this trend did not differ between patients with or without specific comorbidities. Initial treatment with an ARB increased from 4% in 1996 to 12% in 2000, mostly at the expense of ACE-I and calcium channel blockers. In all years, approximately 30% of the newly treated hypertensive patients without any relevant comorbidity received an ACE-I or an ARB as initial treatment. These findings confirm that these antihypertensive drugs are used whereas long-term benefits are still uncertain and sufficient evidence-based alternatives are available. On the other hand, the differences in prescribing patterns between ACE-I and ARBs suggest that increases in use of new drugs shortly after their introduction are largely not specific but, in later years, are confined to patients for whom this is more evidence-based.

Previous studies demonstrated that, between 1980 and 1998, the use of diuretics and beta-blockers declined whereas the use of ACE-I (sometimes including ARBs) increased for treatment of hypertension.[10-15] Our study shows that this pattern is more complicated when differentiating for ACE-I and ARBs, and also for specific subgroups of patients. The relevance of these subgroups was already supported by studies indicating that ACE-I were more commonly prescribed to hypertensive patients with diabetes, hypercholesterolemia, heart failure, history of myocardial infarction or angina pectoris.[11-13;20;21] Looking at the influence of comorbidity during our whole study period, we could confirm some of these associations. Diabetes was the most important predictor, especially for initial ACE-I and ARB use. Hypertensive patients with diabetes were almost four-fold more likely to receive an initial treatment with ACE-I, and two-fold more likely to receive initial ARB treatment. ACE-I use was also higher in patients with heart failure, proteinuria and/or renal insufficiency, but this association diminished after adjusting for specialists' influences. Previous studies that did not correct for this influence may therefore have overestimated the actual influence of some of these comorbidities. By contrast to previous studies, we found a negative association with ACE-I use for patients with a history of myocardial infarction or angina pectoris. This is not surprising because we compared ACE-I users to all users of classic antihypertensives, including beta-blockers, whereas other studies used only diuretics as reference category.[11-13] The positive association between patients with hypercholesterolemia and the use of ACE-I and ARB is consistent with previous findings.[11] There are no specific recommendations for the hypertension treatment of this group of patients, and there is no clear reason for especially prescribing ACE-I in patients with this additional risk factor. One possible explanation might be that thiazide diuretics are less favoured for these patients based on reports that they could induce small increases in cholesterol levels.[27] Finally, where other studies already reported that hypertensive patients with asthma and/or COPD were less likely to receive beta-blockers[11;12], it became clear from our study that ARBs are used more often as (initial) antihypertensive treatment for these patients. Although none of the guidelines recommend ARBs for these patients, physicians may be more inclined to use these drugs to avoid bronchospasm caused by beta-blockers.[28]

An important strength of our study is that we used data from a large, longitudinal database comprising information about diagnoses and prescriptions on a patient level. This allowed us to look at the influence of various patient characteristics on both initial and prevalent use of ACE-I and ARBs. In addition, we adjusted for referrals to disentangle the effect of specialists' prescribing from the effect of comorbidity on prescribing patterns in general practice. This is relevant because we observed that patients referred to an internist or cardiologist were more likely to be prescribed ACE-I and ARBs, and medication initiated by specialists is frequently continued by GPs.[29]

A limitation of this study is the lack of a specific diagnosis for each medication. As with many cardiovascular drugs, the agents followed in this study may be indicated for the treatment of

various diseases. From the GP records, it was not always possible to ascertain the cardiovascular diagnosis for which a particular drug was being used, and one drug may be prescribed to simultaneously treat more than one cardiovascular disease in an individual patient. However, each of the patients included in this study had a diagnosis of hypertension registered in their GP record. Given this, we can assume that the cardiovascular medications included in this study were either prescribed directly for hypertension or to treat a combination of hypertension and some coexisting conditions.

In conclusion, the use of ACE-I and ARBs is partly related to several comorbidities, only some of which are clearly evidence-based. Although, ACE-I use was similar in the different patient groups in 1996, it increased by the year 2000 in hypertensive patients with comorbidities for which its use has been recommended. By contrast, trends in prescribing of ARBs are not in agreement with evidence-based guidelines at that time. ARB use significantly increased immediately after its introduction in 1995 in hypertensive patients with and without comorbidities. Apparently, these newer antihypertensive agents are considered as a first-choice drug in a non-selective group of hypertensive patients. The steep rise in ARB use might be caused by specific GPs and related to a greater reliance on drug company information or susceptibility to follow the specialists' lead in the use of new drugs, as suggested previously.[30]

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Appendix

The ICPC codes [22] and ATC codes [23] shown in the following table were used to assess presence of (co)morbidity.

	ICPC codes	ATC codes
angina pectoris	K74	
ankle oedema	K09	
arrhythmia	K78, K79, K80, K84.3, K84.4	C01B
asthma / COPD	R95, R96	
diabetes	T90	A10
gout	T92	M04
heart failure	K77	
hypercholesterolemia	T93	B04, C10
hypertension	K85, K86, K87	
myocardial infarction	K75, K76	
proteinuria / renal insufficiency	U98.1, U99.1	
stroke	K89, K90	

COPD, chronic obstructive pulmonary disease; ICPC, International Classification for Primary Care; ATC, anatomical therapeutical chemical classification.

Chapter 3

Uptake of Angiotensin II Receptor Blockers in the treatment of hypertension

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European Journal of Clinical Pharmacology 2005; 61: 461-466

Abstract

Objective

To examine trends in prescribing of Angiotensin II Receptor Blockers (ARBs) as initial and second-line treatment of hypertension.

Methods

We performed a cohort study in the Integrated Primary Care Information database, a general practice research database in The Netherlands. We included hypertensive patients who were newly treated with antihypertensive drugs between 1996 and 1999. Initial treatment was defined as the first prescribed antihypertensive drug after diagnosis of hypertension. As second-line treatment we considered prescriptions of a second antihypertensive drug class, either as switch or addition. We used logistic regression and Cox proportional hazard analysis to estimate time trends in use of ARBs as initial or second-line treatment.

Results

In total, 8% of the 3,102 newly treated hypertensive patients received ARBs as initial treatment. Initial ARB use increased significantly from 4% to 10% during the period 1996-1999, whereas calcium channel blocker and angiotensin-converting enzyme inhibitor (ACE-I) use decreased. ARBs were used as second-line treatment in less than 4% of 2,544 patients who were initially treated with an antihypertensive drug other than an ARB: 2% switched to an ARB (mostly from ACE-Is) and 1% received ARBs as add-on treatment. Diuretics and beta-blockers were used five to ten times more often as add-on treatment than ARBs.

Conclusion

ARBs achieved a position in the treatment of hypertension as initial rather than second-line therapy.

Introduction

Angiotensin II Receptor Blockers (ARBs) form the newest class of antihypertensive agents, which have been available in The Netherlands since 1995. Their efficacy in lowering blood pressure is comparable to other antihypertensive drug classes, but they are suggested to be better tolerated and therefore are an attractive option for the treatment of hypertension.[1-3] During the first years after their introduction, however, there was no evidence from large clinical trials about their benefits on cardiovascular morbidity and mortality. In 2001 benefits of ARBs were demonstrated in patients with heart failure, and in hypertensive patients with coexisting diabetes, proteinuria or microalbuminuria.[4-7] The first clinical trial looking at hard endpoints in a large group of patients with essential hypertension was published in 2002.[8] Recently, doubts were raised regarding long term safety of ARBs.[9] Therefore, in most national and international hypertension guidelines, ARBs have no place as initial treatment in hypertension and are only recommended as second-line treatment in patients who require angiotensin-converting enzyme inhibitors (ACE-Is) but do not tolerate them.[10;11] Patients for whom ACE-Is are preferred are those with coexisting heart failure, diabetes, proteinuria or renal insufficiency.

Several studies have shown the discrepancy between prescribing patterns in hypertension and guideline recommendations.[12;13] These studies did not include ARBs as (separate) drug class. Also, studies describing initial and second-line use of antihypertensive drugs did not provide specific information on ARB use.[14-16] Recently, it was shown that prescribing of ARBs increased rapidly in the late 1990s, but it is unclear to what extent this involves initial or second-line therapy for hypertension.[17;18]

The objective of this study was to examine trends in prescribing of ARBs as initial and second-line treatment of hypertension in the years after their introduction on the market.

Methods

Setting

We used data from the Integrated Primary Care Information (IPCI) database from the Erasmus Medical Center in The Netherlands. This is a longitudinal general practice research database containing the complete electronic medical records from more than 100 participating Dutch general practitioners (GPs). The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses (using the International Classification for Primary Care (ICPC)[19] and free text), laboratory findings, referrals and drug prescriptions. To maximise completeness of the data, GPs who contribute to the IPCI database are not permitted to use paper-based records. The database complies with European Union

guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research in several studies that evaluated the quality of the available data.[20]

Study period and population

In this cohort study, we included patients with a diagnosis of hypertension who were newly treated with antihypertensive drugs between 1 January 1996 and 31 December 1999, following the introduction of the first ARB on the Dutch market in March 1995. Hypertension was defined as a coded diagnosis of hypertension (ICPC: K85, K86, K87)[19] or a free text listing of hypertension in the patient record. This latter group was manually evaluated to include only those patients where hypertension was mentioned as their diagnosis. Patients were excluded if they already had received antihypertensive drugs in the 6 months preceding their diagnosis of hypertension.

Definitions of initial and second-line treatments

As initial treatment, the first prescription of antihypertensive drug therapy within the 6 months after diagnosis of hypertension was classified as a diuretic, beta-blocker, calcium channel blocker, ACE-I, ARB or combination of these (fixed or co-administered). The course of antihypertensive therapy was followed for 1 year to determine which second-line treatment was started after initial monotherapy. Second-line treatment was defined as the second step in the treatment strategy, which can consist of a switch to or an addition of a different antihypertensive drug class. We chose a follow-up period of 1 year, because most changes in antihypertensive treatment occur during the first year of treatment.[21] To characterize the course of treatment, four mutually exclusive categories were distinguished depending on the timing and type of subsequent antihypertensive drug prescriptions: continuation, discontinuation, switch or add-on treatment. *Continuation* was defined as receiving a repeat prescription for the initial drug class at least every 6 months and no prescription for any other antihypertensive drug class during follow-up. *Discontinuation* was defined as having no prescription for any antihypertensive drug class during the 6 months following the date of the last prescription of the initial drug class. A *switch* in treatment was considered if an alternative antihypertensive drug class was prescribed within 6 months after a discontinuation of the initial drug class. *Add-on* treatment was defined as receiving a prescription for a different antihypertensive drug class in addition to a prescription of the initial drug class, simultaneously or in the following 3 months.

Data analyses

A descriptive analysis characterized the study population and defined subgroups according to calendar year and type of initial antihypertensive drug treatment. Differences in patient characteristics between year cohorts were tested using chi-square tests. To assess whether the

initial treatment changed over the study years, odds ratios for calendar year were estimated using logistic regression analysis adjusting for age and sex. Separate models were run for each antihypertensive drug class. To compare second-line treatment in different year cohorts, Cox proportional hazard analysis was used to calculate age- and sex-adjusted hazard ratios for each drug class. This analysis takes possible differences in follow-up time into account. Subgroup analyses were conducted excluding patients with prevalent comorbid conditions that may affect ARB use, i.e. heart failure, diabetes, proteinuria and/or renal insufficiency.

Results

We identified 3,102 hypertensive patients who received an initial antihypertensive treatment. Patients had a mean age of 58 years and 58% were female (**Table 1**). Patients who started antihypertensive treatment later during the study period were somewhat younger (chi-square test $P = 0.153$). The proportion of male patients increased significantly from 37% in 1996 to 45% in 1999 (chi-square test $P = 0.017$). Hypertensive patients with heart failure, diabetes, proteinuria and/or renal insufficiency represented 14% of the study population.

Table 1 Characteristics of the study population and percentages* of initial antihypertensive drug use according to sex, age and year cohort.

	n (%)	% Diuretics	% Beta-blockers	% CCBs	% ACE-Is	% ARBs	% Combination therapy
Sex							
Male	1,293 (42)	12.8	33.3	10.1	23.7	8.7	11.3
Female	1,809 (58)	26.6	31.1	8.3	17.5	6.7	9.8
Age							
18 to 49	842 (27)	16.6	43.0	6.2	21.5	6.8	5.9
50 to 59	780 (25)	17.8	38.8	7.6	18.5	7.3	10.0
60 to 69	676 (22)	20.1	26.9	10.4	21.2	9.8	11.7
70 to 79	586 (19)	26.8	19.6	12.5	20.1	7.0	14.0
80+	218 (7)	34.4	14.2	12.4	17.0	6.0	16.1
Year cohort							
1996	550 (18)	18.2	31.3	11.6	23.1	3.8	12.0
1997	670 (22)	17.2	32.4	12.7	21.3	7.0	9.4
1998	858 (28)	20.3	33.2	8.3	19.8	7.6	10.8
1999	1,024 (33)	25.2	31.2	6.0	17.9	9.9	10.0

CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. * Percentages of row total; percentage of column total between brackets.

Table 2 Time trends in the initial use of different antihypertensive drug classes in 3,102 hypertensive patients.

	Adjusted odds ratios (95% confidence interval)							
	1996		1997		1998		1999	
Diuretics	1	(reference)	1.0	(0.7-1.3)	1.2	(0.9-1.6)	1.7	(1.3-2.2)*
Beta-blockers	1	(reference)	1.0	(0.8-1.3)	1.1	(0.8-1.3)	0.9	(0.7-1.2)
CCBs	1	(reference)	1.1	(0.8-1.6)	0.7	(0.5-1.0)*	0.5	(0.3-0.7)*
ACE-Is	1	(reference)	0.9	(0.7-1.2)	0.8	(0.6-1.0)	0.7	(0.5-0.9)*
ARBs	1	(reference)	1.9	(1.1-3.2)*	2.0	(1.2-3.3)*	2.7	(1.7-4.4)*
Combination therapy	1	(reference)	0.8	(0.5-1.1)	0.9	(0.6-1.3)	0.8	(0.6-1.2)

CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Odds ratios for calendar year were adjusted for sex and age. Separate models were run for each antihypertensive drug class. * Significant at $P < 0.05$ level

Table 3 Treatment after 1 year in patients who were initially treated with antihypertensive monotherapy.

	Initial antihypertensive drug treatment												
	DIU		BB		CCB		ACE-I		ARB		Total		*P* value
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	
Patients (total)	647		993		281		623		234		2778		
Continuation	150	(23)	341	(34)	91	(32)	185	(30)	83	(35)	850	(31)	< 0.001
Discontinuation	255	(39)	290	(29)	83	(30)	162	(26)	52	(22)	842	(30)	< 0.001
Switch	83	(13)	87	(9)	48	(17)	96	(15)	22	(9)	336	(12)	< 0.001
Add-on	102	(16)	191	(19)	38	(14)	131	(21)	59	(25)	521	(19)	0.002
Incomplete follow-up	57	(9)	84	(8)	21	(7)	49	(8)	18	(8)	229	(8)	0.943

DIU, diuretic; BB, beta-blocker; CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. *P* values refer to comparisons between patients groups who initially received different antihypertensive drug classes (ANOVA).

Initial antihypertensive treatment

Initial use of each antihypertensive drug class differed between various patient subgroups, e.g. by sex and age (**Table 1**). Examination of time trends of initial antihypertensive treatment demonstrated marked changes between 1996 and 1999: the percentage of ARBs as initial treatment increased from 4% to 10%, diuretics increased from 18% to 25%, whereas use of calcium channel blockers fell from 12% to 6%, and ACE-Is from 23% to 18%. These time trends remained significant after adjustment for sex and age (**Table 2**). Initial use of beta-blockers remained stable over the years (31%). Also, initial use of combination therapy remained stable, but there was a significant increase of combination therapies consisting of ARBs (from 0.2% to 2%). Restriction of the analyses to hypertensive patients without heart failure, diabetes, proteinuria and/or renal insufficiency showed similar time trends in initial use of ARBs (data not shown). During the first year of follow-up, 31% of patients continued their initial treatment, 30% discontinued treatment, 12% switched therapy, 19% received add-on therapy, and 8% did not have 1 year of follow-up (**Table 3**). Initial users of ARBs discontinued treatment less frequently (22%) than those who started on diuretics (39%), beta-blockers (29%), calcium channel blockers (30%) or ACE-Is (26%). Initial users of ARBs had a slightly lower proportion of switches, but received somewhat more add-on therapies than initial users of other antihypertensive drug classes (**Table 3**).

Second-line antihypertensive treatment

Of the 2,544 patients who were initially treated with an antihypertensive drug other than an ARB, 59 patients switched to ARBs (2.3%). This rate is comparable to the percentages of switches to diuretics and calcium channel blockers (**Table 4**). Switches to beta-blockers (5.4% of patients starting on another drug) and ACE-Is (4.3%) occurred about twice as often. Of the 59 switches to an ARB, 32 originated from initial ACE-I use (54%). Hypertensive patients without heart failure, diabetes, proteinuria and/or renal insufficiency switched just as much to ARBs (on average 2.4%) as patients with these comorbidities. Percentage of switches to ARBs increased significantly from 1.1% in 1996 to 3.0% in 1997, but decreased again to 1.7% in 1999. The same pattern was observed in the Cox regression analysis when we accounted for variable follow-up time (**Table 5**).

Of the 2,544 patients who were initially treated with an antihypertensive drug other than an ARB, 36 patients received ARBs as add-on treatment (1.4%). Hypertensive patients without heart failure, diabetes, proteinuria and/or renal insufficiency received comparable percentages of ARBs as add-on treatment (1.3%). Add-on therapies with other drug classes were far more common than with ARBs, especially the addition of diuretics (11.7% of patients starting on another drug) and beta-blockers (6.5%). The percentage of add-on treatment with ARBs increased gradually from 0.4% in 1996 to 2.2% in 1999; patients in cohort 1999 received significantly more often ARBs as add-on treatment than those in 1996 (**Table 6**).

Table 4 Second-line treatment choice: switches and add-on therapy.

	Initial antihypertensive drug treatment											
	DIU		BB		CCB		ACE-I		ARB		total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Switch (total)*	83	(13)	87	(9)	48	(17)	96	(15)	22	(9)	336	(12)
to DIU	-		16	(2)	12	(4)	14	(2)	7	(3)	49	(2)
to BB	35	(5)	-		20	(7)	32	(5)	10	(4)	97	(5)
to CCB	12	(2)	17	(2)	-		19	(3)	3	(1)	51	(2)
to ACE-I	28	(4)	44	(4)	17	(6)	-		3	(1)	92	(4)
to ARB	8	(1)	15	(2)	4	(1)	32	(5)	-		59	(2)
Add-on (total)*	102	(16)	191	(19)	38	(14)	131	(21)	59	(25)	521	(19)
with DIU	-		121	(12)	14	(5)	76	(12)	39	(17)	250	(12)
with BB	56	(9)	-		16	(6)	30	(5)	14	(6)	116	(6)
with CCB	7	(1)	34	(3)	-		18	(3)	5	(2)	64	(3)
with ACE-I	33	(5)	30	(3)	6	(2)	-		1	(0)	70	(3)
with ARB	10	(2)	11	(1)	3	(1)	12	(2)	-		36	(1)

DIU, diuretic; BB, beta-blocker; CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. * Switches or add-on therapies to combinations of two different antihypertensive drug classes are counted in both classes (n=27). Therefore, the numbers in each column may add up to more than the total of switches or add-on therapies.

Table 5 Time trends in second-line treatment of different antihypertensive drug classes due to a treatment switch.

	Adjusted hazard ratios (95% confidence interval)							
	1996		1997		1998		1999	
Diuretics	1	(reference)	1.7	(0.7-4.5)	1.6	(0.6-4.2)	1.8	(0.7-4.6)
Beta-blockers	1	(reference)	0.8	(0.4-1.6)	1.0	(0.6-1.9)	1.1	(0.6-2.0)
CCBs	1	(reference)	1.7	(0.7-4.0)	0.8	(0.3-2.0)	1.0	(0.4-2.4)
ACE-Is	1	(reference)	0.7	(0.4-1.3)	0.6	(0.3-1.0)	0.6	(0.3-1.0)
ARBs	1	(reference)	2.8	(1.0-7.5)*	3.0	(1.2-8.0)*	1.6	(0.6-4.5)

CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Hazard ratios for calendar year were adjusted for sex and age. Separate models were run for each of the five drug classes. * Significant at $P < 0.05$ level

Table 6 Time trends in second-line treatment of different antihypertensive drug classes due to add-on treatment.

	Adjusted hazard ratios (95% confidence interval)							
	1996		1997		1998		1999	
Diuretics	1	(reference)	1.3	(0.9-1.9)	1.2	(0.8-1.8)	1.1	(0.7-1.6)
Beta-blockers	1	(reference)	1.1	(0.6-2.2)	1.7	(0.9-3.2)	1.7	(0.9-3.1)
CCBs	1	(reference)	0.8	(0.3-2.0)	1.2	(0.5-2.5)	1.2	(0.6-2.6)
ACE-Is	1	(reference)	1.3	(0.6-2.9)	1.1	(0.5-2.4)	1.3	(0.6-2.7)
ARBs	1	(reference)	3.3	(0.7-15.6)	2.7	(0.6-12.8)	5.5	(1.3-23.6)*

CCB, calcium channel blocker; ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker. Hazard ratios for calendar year were adjusted for sex and age. Separate models were run for each of the five drug classes. * Significant at $P < 0.05$ level

Discussion

This study provides an overview of the uptake of ARBs in the treatment of hypertension in The Netherlands. Initial use of ARBs increased substantially in the years following their introduction, mostly at the expense of calcium channel blockers and ACE-Is. The use of ARBs as second-line treatment was much lower. In 1999, more than 10% of the newly treated hypertensive patients received an ARB as initial treatment, whereas less than 4% of all patients who were initially treated with another antihypertensive drug received an ARB as second-line therapy in the following year. Switching to an ARB occurred slightly more often than the addition of an ARB as second-line treatment, but we did observe an increasing rate of add-on treatments with ARBs by the year 1999. Patients who switched to ARBs mostly came from initial treatment with an ACE-I. Beta-blockers and diuretics remained the most common initial and second-line treatment choice in The Netherlands.

If guideline recommendations had been followed during our study period, one would have expected ARBs to be prescribed mostly as second-line treatment, especially in patients unable to tolerate ACE-I.[10;11] Contrary to these expectations, ARBs were not very popular as second-line treatment, but instead achieved a significant position as initial treatment for hypertension. As we reported elsewhere, this position was not restricted to patients with relevant comorbidities.[18] ARBs were already used as initial treatment in uncomplicated hypertensive patients before trials on cardiovascular endpoints became available. A previous study indicated a similar pattern regarding ACE-Is shortly after their introduction.[18] While the prescribing of ACE-Is seems to have developed into a pattern that is more in accordance with guideline recommendations [18], this appears not (yet) to be the case for the ARBs.

Studies showing that ARBs are better tolerated and have higher persistence rates than other antihypertensive drug classes probably encouraged prescribing of these newer drugs as the initial treatment.[22;23] It is likely that promotional activities of the pharmaceutical industry accelerated the dissemination and adoption of these views.[24] Pharmaceutical companies in The Netherlands devoted substantial resources to promote the advantages of ARBs in terms of efficacy and tolerability.[24] For pharmaceutical companies, there was a lot at stake when patents of a number of antihypertensive drugs, mainly ACE-Is, expired. For GPs, however, there were no restrictions to prescribe the newer, more expensive drugs or incentives to prescribe generic drugs at that time.

Another factor in the uptake of new drugs concerns the influence of specialists. Especially for cardiovascular drugs, a substantial impact has been observed on the GPs' prescribing.[24] In The Netherlands, prescriptions initiated by specialists are often continued by GPs. This obviously affects the prevalent use of ARBs in general practice.[18] In this study, however, we looked at first prescriptions within 6 months after a diagnosis of hypertension. These will mostly be prescriptions initiated by the GPs themselves. Moreover, the rapid increase in the use of ARBs immediately after their introduction on the market also suggests that GPs have started to prescribe these drugs at their own initiative.

The increased initial treatment with ARBs occurred at the expense of calcium channel blockers and ACE-Is. The debate on controversial results regarding the safety of calcium channel blockers around 1996 may have played a role in the decreased prescribing of calcium channel blockers.[24] The increased rate of ARBs as add-on therapy may be a result of an intensified treatment of hypertension. Guidelines recommend the addition of a second drug from a different class when adequate blood pressure levels are not achieved. However, only one in every five patients received an add-on therapy in the first year of treatment. This confirms the findings from previous studies showing that hypertension is undertreated in The Netherlands.[22;23] Moreover, 30% of all newly treated patients discontinued treatment in the first year, which is similar to results from other studies.[14-16] This implies that there is still much room for improvement in hypertension treatment.

This study is the first which focuses on the uptake of ARBs in the treatment of hypertension, and made a distinction between initial and second-line treatment. Other studies which described prescribing patterns of initial and second-line antihypertensive drugs gave no clear information on ARB use.[14-16] A strength of this study is that we used routinely collected data from a large, longitudinal general practice database comprising information about diagnosis and prescriptions at the patient level. This allowed us to follow dynamics in prescribing patterns in cohorts of individual newly treated hypertensive patients in the years following the introduction of ARBs. A limitation of this study lies in our definitions of initial and second-line treatment. We identified changes in treatment in a period of 6 months, which is a commonly

used time window. This covers twice the maximum period of 3 months that may be supplied by one prescription for antihypertensive drugs in The Netherlands.

Although this study focused on the uptake of ARBs, it may have implications for understanding the adoption process of other new therapeutic drug classes. It appears that newer, more expensive drug classes are chosen soon after their introduction on the market, not primarily for patients who do not respond satisfactorily to previous treatment, but often in newly treated patients without specific reasons. Since benefits on hard endpoints are often not established and also long-term risks are not known, this may have important consequences on health care.

In conclusion, ARBs have achieved a position in the treatment of hypertension as initial rather than second-line therapy which is not in accordance with the existing guideline recommendations for hypertension.

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Chapter 4

Hyperlipidemia and hypertension management in type 2 diabetes patients between 1998-2004: longitudinal observational study

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Submitted

Abstract

Objective

To assess trends in risk management and identify determinants for medication adjustments in type 2 diabetes patients with uncontrolled hypertension and/or hyperlipidemia.

Methods

We conducted a retrospective cohort study using data from the Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC)-study in The Netherlands. Management of hypertension and hyperlipidemia was assessed yearly from 1998-2004 by measuring the percentage of patients receiving a treatment initiation or intensification (dose increase or additional drug class added) among all patients with elevated risk factor levels.

Results

During the study period, the percentage of patients with elevated TC/HDL ratio (> 6) decreased considerably (from 29% to 4%) whereas the percentage of hypertensive patients decreased only slightly (≥ 150/85mmHg; from 58% to 51%). Initiation of lipid-lowering therapy, and both initiation and intensification of antihypertensive therapy was higher in more recent years. However, still two-third of patients with insufficiently controlled blood pressure in 2003 did not receive an initiation or intensification of antihypertensive treatment in the following year. Treatment changes were mainly triggered by elevated levels of the corresponding risk factor. We did not observe increased initiation rates for lipid-lowering therapy in patients with both hypertension and hyperlipidemia.

Conclusions

Hypertension and hyperlipidemia management in type 2 diabetes patients has improved in the past decade but further improvement is possible. Greater effort is especially needed to stimulate medication adjustments in patients with insufficiently controlled and combined risk factors.

Introduction

The increased incidence of cardiovascular disease (CVD) among patients with type 2 diabetes has led to increased recognition of hypertension and hyperlipidemia as important targets of therapy in addition to hyperglycemia.[1;2] Clinical trials in patients with type 2 diabetes convincingly demonstrated that cholesterol reduction and tight blood pressure control reduce the risk of major cardiovascular events.[3-5] Diabetes guidelines therefore advocate an intensified multifactorial treatment approach and often incorporate risk tables to guide adequate management in the primary prevention of CVD.[6-9] The Dutch General Practitioners' guidelines have recommended a combined assessment of blood pressure and lipid levels to target treatment to patients at high risk for CVD.[6;10] As a result, lipid-lowering therapy is recommended in patients with high lipid ratio levels but also in patient with lower lipid ratio levels who have hypertension. There are doubts, however, that this high-risk approach has been sufficiently implemented in daily practice.[11;12]

In addition, it has been shown that although increasing numbers of diabetes mellitus patients are tested for risk factors, much smaller percentages reach target goals.[13-15] These findings might be explained by low rates of medication initiation and dose adjustment in patients with elevated risk factor levels.[14;16-18] Up to now, however, drug regime changes in type 2 diabetes patients have only been studied over short time periods, not allowing for the assessment of trends.[14;16;18] Insight into changes in drug regime initiation and intensification over time can help us guide future efforts to improve the quality of diabetes care.

In this article we present trends in initiation and intensification of lipid-lowering and antihypertensive drug therapy in type 2 diabetes patients during 1998-2004. We examine predictors of drug regime changes, and in particular whether patients with hypertension and hyperlipidemia are more likely to receive an initiation of lipid-lowering therapy.

Methods

Setting

This study was conducted as part of an ongoing longitudinal study, the Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC)-study in The Netherlands. The ZODIAC-study is a shared-care project for type 2 diabetes within the primary setting that started in 1998. Details about design have been published previously.[19] In brief, general practitioners (GPs) are supported by hospital-based diabetes specialist nurses (DSNs) for the annual control of type 2 diabetes patients. The GPs kept the full responsibility for the care of the patients and remained responsible for the check-ups that should take place every three months. The number of participating GPs ranged from 32 in 1998 to 46 in 2004.

Study subjects

The study population represents a dynamic cohort of type 2 diabetes patients who had at least two visits in consecutive years for their annual control to a DSN between 1998 and 2004. Patients were included when they met the following criteria in the judgement of the GP: (1) they had known type 2 diabetes mellitus, according to the Dutch diabetes guidelines; (2) they were treated exclusively in primary care; (3) they had no terminal illness, and (4) they had no severe deficits in memory and understanding.

Measurements

The annual visit to the DSN included registration of the following data: (1) medication use (general and diabetes medication) and medical history as provided by the GP and checked with the patient; (2) height, weight, blood pressure measured at the visit; and (3) laboratory values that had been measured before the visit. The laboratory measurements were glycosylated haemoglobin (HbA1c), total cholesterol (TC), high-density lipoproteins (HDL) and low-density lipoproteins (LDL). All laboratory measurements were performed in a central laboratory. Medical history included year of diabetes onset and history of myocardial infarction and/or angina pectoris. Body mass index was calculated from weight and length (kg/m^2). The TC/HDL ratio was calculated from total cholesterol and HDL cholesterol.

Guideline recommendations

According to the Dutch General Practitioners' guideline for diabetes effective during our study period, patients with hypertension (systolic blood pressure (SBP) $\geq$ 150 mmHg or diastolic blood pressure (DBP) $\geq$ 85 mmHg) should be treated with antihypertensive drugs.[6;20] Lipid-lowering therapy should be targeted to patients at greatest risk for CVD: i.e. patients with pre-existing CVD, patients with a (suspected) hereditary lipid disorder or patients with a 10-year coronary heart disease (CHD) risk larger than 25%.[6;10] To eliminate the need for GPs to calculate risk scores, the guidelines incorporate colour-coded risk tables that indicate the predicted CHD risk and guide management for primary prevention based on a person's age, sex, smoking status, blood pressure, and TC/HDL ratio. From these tables, it can be derived that the presence of hypertension determines the need for lipid-lowering treatment in non-smoking patients with a TC/HDL ratio of 5-7, and in smoking patients with a TC/HDL ratio of 4-6. The guideline, however, also provides two simplified recommendations for the primary prevention: men aged 50-70 years and women aged 50-75 years should receive lipid-lowering therapy when their TC/HDL ratio is higher than 6 for non-smoking patients and when their TC/HDL ratio is higher than 5 for smoking patients.[6]

Changes in drug therapy

Using the prescribing information from reports of annual controls by the DSNs, we determined for each patient in each year whether the patient had received an initiation or intensification of

drug therapy. Drug therapy was considered to have been intensified if the dose was increased or an additional drug class was added. A switch to another drug class without continuation of the original medication was not considered as an intensification of therapy, because patients could have been switched due to side effects.

Statistical analyses

Descriptive analyses characterize the population of type 2 diabetes patients over time, and show the frequencies of drug regime initiations and intensifications in patients with elevated risk factor levels. To identify determinants for initiation and intensification of lipid-lowering and antihypertensive drug therapy, generalized estimating equation analyses were performed using STATA 8. With generalized estimating equation analysis, the relation between longitudinally measured variables can be studied correcting for within person correlations caused by the repeated measurements for one subject. Models were constructed for the changes in antihypertensive treatment and changes in lipid lowering treatment, and for initiation and intensification separately. We assessed the influence of the following factors: age, gender, SBP, DBP, TC/HDL ratio and TC. Factors that contributed significantly ($P < 0.05$) to the model were maintained in the final model (forward stepwise regression). To test a possible combined effect of blood pressure and lipid levels, an interaction term of SBP with TC/HDL ratio was included in the models. We adjusted for HbA1c, diabetes duration, history of myocardial infarction and/or angina pectoris, and body mass index. Because initiation of lipid-lowering treatment was only recommended in men younger than 70 years and women younger than 75 years, we repeated analyses for lipid-lowering therapy on only these patients. Results are presented as odds ratios (OR) with corresponding confidence intervals (CI).

Results

Characteristics of the study cohort

The study population ranged from 946 to 1485 type 2 diabetes patients over the years 1998 to 2003. Mean age was 67 years and women represented the majority (57%) of the study population (**Table 1**). The median duration of diabetes was 5 years and remained reasonably stable over the years. Overall, 65% of the patients was treated with oral hypoglycaemic drugs only, and 15% received a combination of oral hypoglycaemic drugs and insulin or insulin alone. We observed an increase in the use of lipid-lowering drug treatments (from 12% to 34%) and antihypertensive drug treatments (from 48% to 69%) and substantial decreases in mean HbA1c, TC/HDL ratio, and systolic blood pressure values between 1998 and 2003 (**Table 1**).

Table 1 Characteristics of type 2 diabetes patients

	1998 N=946	1999 N=1075	2000 N=1248	2001 N=1374	2002 N=1295	2003 N=1485
Patient characteristics						
Age (years)	68 ± 11	68 ± 11	67 ± 11	67 ± 11	67 ± 11	67 ± 11
Female sex (%)	57%	58%	57%	57%	57%	55%
Duration of diabetes (years)	5 (2-10)	5 (2-10)	5 (2-10)	4 (2-9)	4 (2-9)	5 (2-9)
History of MI/AP	25%	22%	21%	19%	18%	18%
Body mass index (kg/m^2)	29.0 ± 4.7	29.0 ± 4.7	29.4 ± 4.8	29.5 ± 4.8	29.5 ± 4.7	29.5 ± 4.8
HbA1c (% units)	7.5 ± 1.2	7.4 ± 1.2	7.3 ± 1.3	7.0 ± 1.2	7.0 ± 1.2	7.0 ± 1.2
TC/HDL ratio	5.3 ± 1.6	4.8 ± 1.3	4.5 ± 1.2	4.4 ± 1.2	4.1 ± 1.1	3.9 ± 1.1
Systolic blood pressure (mmHg)	155 ± 25	150 ± 23	150 ± 23	146 ± 20	145 ± 21	148 ± 21
Diastolic blood pressure (mmHg)	84 ± 11	82 ± 11	81 ± 11	80 ± 10	80 ± 10	84 ± 11
Number of glucose-lowering drugs						
None	20%	17%	18%	20%	23%	20%
1 oral	43%	43%	41%	39%	36%	39%
≥ 2 oral	22%	25%	26%	26%	28%	26%
insulin (with or without oral drugs)	15%	15%	15%	15%	13%	14%
Use of cardiovascular drugs						
Lipid-lowering drugs	12%	15%	22%	27%	30%	34%
Antihypertensive drugs	48%	51%	57%	63%	66%	69%
ACE inhibitors or ARBs	24%	26%	30%	36%	42%	45%
Antiplatelet drugs	22%	22%	23%	25%	25%	26%

Values are percentages, means ± standard deviations or median (interquartile range). MI, myocardial infarction; AP, angina pectoris; HbA1c, haemoglobin A1c; TC, total cholesterol; HDL, high-density lipoprotein; ACE inhibitors, angiotensin-converting enzyme inhibitors; ARBs, angiotensin II receptor blockers.

Management of hyperlipidemia

From 1998 to 2003, the percentage of patients with elevated TC/HDL ratio (> 6) decreased considerably from 29% (273/939) to 4% (59/1471). Of these patients, 9% (25/273) were on lipid-lowering drug therapy in 1998 and 25% (15/59) in 2003 (**Table 2**). Among untreated patients with elevated TC/HDL values, significant improvements occurred in the percentage of patients who started on lipid-lowering therapy (12% in 1999 vs. 35% in 2004). Of those uncontrolled patients already on therapy, most had no intensification of their lipid-lowering drug therapy (12% in 1999 vs. 7% in 2004). In multivariable analyses, TC/HDL ratio, SBP, age, history of myocardial infarction and/or angina pectoris, and year of screening were predictors of subsequent initiation of lipid-lowering therapy, while gender was not found to be associated with treatment initiation (**Table 3**). There was no significant interaction between TC/HDL values and SBP levels, suggesting that the association between TC/HDL ratio and subsequent initiation of lipid-lowering therapy does not differ by SBP levels.

Table 2 Changes in lipid-lowering and antihypertensive drug regimes from 1998 to 2004 in type 2 diabetes patients with elevated risk factor levels.

	1998/1999				2003/2004			
	No intensification	Start / add drug	Increase dose	Total*	No intensification	Start / add drug	Increase dose	Total
Lipid-lowering drug therapy	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)	N
Use of lipid-lowering drugs in patients with TC/HDL > 6								
No	219 (88%)	29 (12%)	-	248	28 (65%)	15 (35%)	-	44
Yes	22 (88%)	1 (4%)	2 (8%)	25	14 (93%)	-	1 (7%)	15
All patients with TC/HDL > 6	241 (88%)	30 (11%)	2 (1%)	273	42 (72%)	15 (26%)	1 (2%)	59

	1998/1999				2003/2004			
	No intensification	Start / add drug	Increase dose	Total	No intensification	Start / add drug	Increase dose	Total
Antihypertensive drug therapy	n (%)	n (%)	n (%)	N	n (%)	n (%)	n (%)	N†
Number of antihypertensive drugs in hypertensive patients‡								
None	213 (80%)	52 (20%)	-	265	146 (71%)	61 (29%)	-	211
1	90 (74%)	22 (18%)	10 (8%)	125	118 (61%)	63 (33%)	22 (11%)	196
2	94 (88%)	8 (7%)	5 (5%)	107	123 (61%)	58 (29%)	28 (14%)	202
≥ 3	40 (85%)	2 (4%)	5 (11%)	47	112 (77%)	19 (13%)	16 (11%)	145
All hypertensive patients	437 (81%)	84 (16%)	20 (4%)	544	499 (67%)	201 (27%)	66 (9%)	754

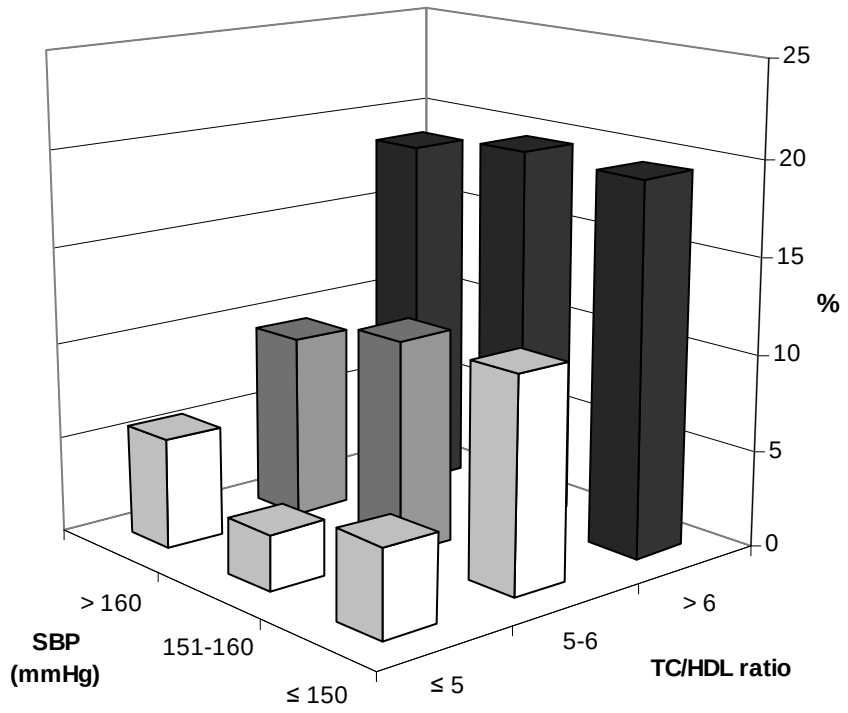
* Numbers in each row may add up to less than the total number of patients in each year due to missing values. † 20 patients with antihypertensive drug therapy intensification in 2003/2004 received both an increase in dose as an addition of a new antihypertensive drug class and are counted in both categories. Therefore, the numbers in each column may add up to more than the total number of patients. ‡ Hypertension was defined as blood pressure > 150/85 mmHg.

Table 3 Multivariable analyses of risk factors associated with initiation and intensification of lipid-lowering and antihypertensive drug therapy in type 2 diabetes patients.

	Lipid-lowering drug therapy				*Antihypertensive drug therapy*			
	Initiation		*Intensification*		*Initiation*		*Intensification*	
	OR_{adj}*	(95% CI)	OR	(95% CI)	OR_{adj}*	(95% CI)	OR_{adj}	(95% CI)
Age (per 10 years)	0.7	(0.6-0.8)	-		1.2	(1.1-1.3)	1.1	(1.0-1.2)
Gender	-		-		-		-	
HbA1c (%)	-		-		0.9	(0.8-1.0)	-	
Systolic blood pressure (per 10 mmHg)	1.1	(1.0-1.1)	-		1.3	(1.3-1.4)	1.1	(1.1-1.2)
Diastolic blood pressure (per 10 mmHg)	-		-		1.2	(1.1-1.4)	1.1	(1.1-1.3)
TC/HDL ratio	1.8	(1.7-2.0)	1.4	(1.2-1.6)	1.2	(1.1-1.3)	-	
History of MI/AP	1.9	(1.4-2.6)	-		2.4	(1.6-3.5)	-	
Year (ref: 1998)								
1999	3.2	(2.1-5.0)	-		2.1	(1.5-3.1)	1.8	(1.3-2.5)
2000	3.5	(2.3-5.4)	-		2.1	(1.4-3.0)	2.2	(1.6-3.0)
2001	3.2	(2.1-5.1)	-		2.4	(1.6-3.5)	2.2	(1.6-3.0)
2002	5.1	(3.3-8.0)	-		2.3	(1.5-3.5)	2.2	(1.6-2.9)
2003	6.1	(4.0-9.6)	-		2.4	(1.6-3.6)	2.2	(1.6-3.0)

Models were constructed for the two drug treatments and for initiation and intensification separately. OR, odds ratio; HbA1c, haemoglobin A1c; TC, total cholesterol; HDL, high-density lipoprotein; MI, myocardial infarction; AP, angina pectoris. * additionally adjusted for body mass index.

Figure 1 Percentage* of patients initiated on lipid-lowering therapy stratified by TC/HDL values and SBP levels.



black bars = lipid-lowering therapy recommended for most patients aged 50-70; grey bars = lipid-lowering therapy recommended for most smoking patients and males aged 60-70 years; white bars = lipid-lowering therapy seldom recommended. * percentage of all patients in each subgroup. SBP, systolic blood pressure; TC, total cholesterol; HDL, high-density lipoprotein.

Accordingly, we observed no difference in the proportion of patients initiated on lipid-lowering therapy who had elevated SBP levels compared to normal SBP levels (**Figure 1**). Only 9% of patients with SBP levels above 160 mmHg and TC/HDL values between 5 and 6 were receiving a treatment initiation, which was not higher than for patients with similar TC/HDL values and SBP levels below 150 mmHg.

Intensification of lipid-lowering therapy was associated with TC/HDL ratio, but not with SBP or other risk factors (**Table 3**). In a subgroup analyses of younger patients (men aged 70 years or younger and women aged 75 years or younger), we found similar point estimates, but age and SBP were not statistically significant determinants anymore. Using total cholesterol as risk factor instead of TC/HDL ratio yielded similar results (data not shown).

Management of hypertension

From 1998 to 2003, the percentage of hypertensive patients (SBP ≥ 150mmHg or DBP ≥ 85 mmHg) decreased from 58% (544/930) in 1998 to 51% (754/1479) in 2003. Of the hypertensive

patients, 51% (279/544) were on antihypertensive drug therapy in 1998 and 72% (543/754) in 2003. Among untreated patients not reaching blood pressure targets, few were started on antihypertensive therapy (20% in 1999 vs. 29% in 2004). Among treated patients not reaching these targets, 19% (52/276) received an intensification of their antihypertensive drug regime in 1999 vs. 35% (186/539) in 2004. As expected, treatment intensifications were less likely to occur in patients taking already two or more antihypertensive drug classes.
In multivariable analyses, subsequent initiation of antihypertensive therapy was positively related to SBP, DBP, TC/HDL ratio, age, history of myocardial infarction and/or angina pectoris, and year of screening, and negatively related to HbA1c. Intensification of antihypertensive drug therapy was positively related to SBP, DBP, age, and year of screening, but not with TC/HDL ratio or other risk factors (**Table 3**).

Discussion

In this large observational study, we observed an overall increased use of antihypertensive and lipid-lowering drugs, and better control of risk factors between 1998 and 2004. The proportion of type 2 diabetes patients who were initiated on lipid-lowering therapy increased substantially, whereas intensification of lipid-lowering therapy hardly changed over time. The proportion of patients initiated on antihypertensive therapy slightly increased, as did the percentage of intensifications in patients already on antihypertensive therapy. Treatment changes were mainly triggered by elevated levels of the corresponding risk factor. We did not observe increased initiation rates for lipid-lowering therapy in patients with hypertension and hyperlipidemia.
Despite these generally favourable improvements in the management of hyperlipidemia and hypertension, still only one-third of patients with insufficiently controlled blood pressure or lipid ratio levels in 2003 received an initiation or intensification of antihypertensive or lipid-lowering treatment in 2004. Other studies have reported similar low rates of treatment initiations, but higher rates of intensifications particularly for lipid-lowering therapy.[14;21;22] In a study in an US academic medical centre in 1997 to 1999, 30% with elevated LDL cholesterol levels received a treatment intensification, and 30% of patients with elevated SBP levels.[22] In a Veterans Affairs study in 1998 to 1999, 39% of patients with diabetes and elevated LDL cholesterol levels received either a treatment initiation or intensification.[21] More recently, a study within a US medical care program in 2002 to 2003 showed even higher rates of therapy initiation or intensification: 64% of patients with insufficiently controlled SBP levels and 47% for insufficiently controlled LDL cholesterol levels.[18] However, their study population included all patients with hypertension, hyperlipidemia, diabetes mellitus or a combination of these conditions. It is known that patients with diabetes receive less intensive antihypertensive and lipid-lowering medication therapy than patients without diabetes.[17] It should be noted that in

our study, the number of patients with insufficiently controlled lipid levels was quite low in the latter years, leaving not much room for further improvement in this group of patients.
Furthermore, we observed that the percentage of lipid-lowering treatment initiations was not higher in patients with elevated blood pressure levels. Results of multivariable analyses also showed that TC/HDL ratio was the strongest predictor of the initiation of lipid-lowering therapy and SBP levels only had a weak effect. More importantly, there was no significant interaction between TC/HDL values and SBP levels, which suggests that the recommended combined assessment of blood pressure and lipid levels has not yet been adopted in clinical practice. Our finding that physicians primarily manage single risk factors is consistent with results from recent studies.[14;23-25]
Several causes have been proposed why physicians may not initiate or intensify therapy appropriately. It has been ascribed to overestimation of care provided, lack of education, training and organizational support necessary in order to achieve therapeutic goals, and lack of adherence with guidelines for risk factor control.[26] Physicians may have been reluctant to prescribe complex medical regimes because of concerns related to side effects, drug interactions, or increased non-adherence. In some cases, physicians may have been reluctant to prescribe additional medicines to those who do not regularly adhere to their current drug regime. Barriers related to the content and format of the cardiovascular risk tables and its recommendations have also been reported, and risk calculator use in still not common.[11;12] The high-risk approach to primary prevention was not always clear to physicians, risk tables were difficult to understand, and physicians were confused by the lack of agreement with other (inter)national risk tables.[11] For many years, different Dutch practice guidelines existed for hyperlipidemia, hypertension and type 2 diabetes, and as a result various guideline recommendations for the prevention of CVD were given.[6;10;20;27-30] For example, the Dutch type 2 diabetes guideline incorporated risk tables but focused on two simplified recommendations with thresholds for TC/HDL ratio to guide decisions for lipid-lowering drugs, while the cholesterol guideline advised to use the risk tables.[6;10] Recently, the Dutch practice guidelines have been brought in agreement with each other: the hypertension and cholesterol guidelines have been combined into a new cardiovascular risk management guideline.[31] In addition, the updated type 2 diabetes guideline now closely follows this cardiovascular risk management guideline.[7] Such integrated guidelines may reduce the lack of consistency and may provide better support for health care practitioners.
A limitation of this study is that we evaluated the management of hyperlipidemia and hypertension within a shared-care project. Hospital-based diabetes specialist nurses, who performed the annual control of type 2 diabetes patients, may have facilitated physicians to provide better care.[19] Our findings may therefore reflect a best-case scenario. Another limitation is that the data were collected on an annual basis. As a result we could not assess whether physicians responded immediately to a visit of an elevated risk factor level. Since

many patients with insufficiently controlled blood pressure or lipid ratio levels did not receive a treatment initiation or intensification in the following year, our results suggests that physicians missed several opportunities to increase medication regimes or dosage. We also did not directly link therapy modifications to clinical outcomes, but several other studies have shown that initiation and intensification of therapy was associated to better levels of control.[32;33] An important strength of this study is that data was collected over a long time period enabling to assess trends in treatment initiation and intensification over a 6-year period. Furthermore, sufficiently detailed medication data was collected to distinguish untreated patients from patients already on therapy.

In conclusion, this study has demonstrated that although management of hypertension and hyperlipidemia has improved in the past decade, further improvement is possible. Greater effort is especially needed to stimulate medication adjustments in patients with insufficiently controlled and combined risk factors.

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Part II

Physician-level factors related to prescribing of cardiovascular drugs

Chapter 5

Determinants for the Adoption of Angiotensin II Receptor Blockers by General Practitioners

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Social Science & Medicine 2006; 63: 2890-2898

Abstract

Objective

Results of studies conducted 10-20 years ago show the prominence of commercial information sources in the adoption process of new drugs. Over the past decade, there has been a growing emphasis on practicing evidence-based medicine in drug prescribing. This raises the question whether professional information sources currently counterbalance the influence of commercial information sources in the adoption process. The aim of this study was to identify determinants influencing adoption of a new drug class, the Angiotensin II Receptor Blockers (ARBs), by general practitioners (GPs) in The Netherlands.

Methods

A retrospective study was conducted to assess prevalent ARB prescribing for hypertensive patients using the Integrated Primary Care Information (IPCI) database. We conducted a survey among all GPs who participated in the IPCI project in 2003 to assess their exposure to commercial and professional information sources, perceived benefits and risks of ARBs, perceived influences of the professional network, and general characteristics. Multilevel logistic regression was applied to identify determinants of ARB adoption while adjusting for patient characteristics.

Results

Data were obtained from 70 GPs and 9470 treated hypertensive patients. A total of 1093 patients received ARBs (12%). GPs who reported frequent use of commercial information sources were more likely to prescribe ARBs routinely in preference to other antihypertensives, whereas GPs who used a prescribing decision support system and those who were involved in pharmacotherapy education were less likely to prescribe ARBs. Other factors that were associated with higher levels of ARB adoption included a more positive perception of ARBs regarding their effectiveness in lowering blood pressure, and working in single-handed practices or in rural areas.

Conclusions

Aside from determinants related to the patient population, adoption of a new drug class among Dutch general practitioners is still determined more by their reliance on promotional information than by their use of professional information sources.

Introduction

There is a lively debate about which medication to choose in hypertensive treatment, fuelled by controversy about possible limitations of large randomized clinical trials and interpretation of their findings as well as by financial interests and concerns.[1;2] Quality improvement programmes stress the relevance of implementing clinical guidelines and practicing evidence-based medicine, governments aim for cost containments, and pharmaceutical industries aim to make more profits.[3] Amidst these forces, physicians have to decide about the place of new antihypertensive drugs. Results of studies that were conducted more than 20 years ago showed the prominence of commercial information sources in the adoption process of new drugs and the minor influence of professional information sources.[4;5] The influence of commercial information is still a matter of concern, but there are few recent empirical studies on the impact of various information sources on drug choice and prescribing behaviour.[6;7] In an environment with a growing emphasis on evidence-based medicine, professional information sources might counterbalance the influence of commercial information sources in the adoption process.

Angiotensin II Receptor Blockers (ARBs) were introduced in the market in 1995 as a new drug class for hypertension after proving efficacy in lowering blood pressure. Evidence on hard endpoints such as cardiovascular morbidity and mortality in patients with hypertension was not available until 2002.[8] Due to this lack of evidence on hard endpoints, the high costs, and the availability of alternatives with proven effectiveness, ARBs have not been recommended as first-line treatment for essential hypertension in most treatment guidelines.[9;10] Nevertheless, the use of ARBs has increased remarkably in the last 10 years.[11;12]

Adoption rates of new drugs vary among physicians and by type of drug.[13-17] The adoption of new treatments in clinical practice is the result of many factors. Based on Rogers' theoretical model for the diffusion of innovations, the following factors can be identified: (1) information sources used, (2) perceived characteristics of the new drug, (3) professional network and norms, (4) general physician characteristics.[18] In addition to this general framework, decision-making theories can help us understand how treatment choices are made on an individual level.[19] Differences in drug choice can be related to different perceived characteristics or expectations about drugs, but also to differences in the relative importance or value assigned to the various drug aspects.[20-22]

Physicians who frequently prescribe new drugs have shown to be less cost-consciousness in prescribing and to rely more on commercial information sources.[23;24] Adoption of new drugs was also found to be associated with physician gender, specialty, medical school, years since graduation, practice location, practice size, and proportion of elderly in the practice.[15;16] On the other hand, characteristics of the patient population of a physician may also determine the need for prescribing new treatments.[25-27] To date, none of the studies looking at determinants

of drug adoption considered the influence of all factors simultaneously and took possible differences in patient populations into account.
The aim of this study was to identify determinants for adoption of ARBs in routine prescribing for hypertension by linking physician related characteristics to their actual prescribing behaviour while adjusting for patient characteristics.

Methods

Setting

The data reported in this study were collected from 75 general practitioners contributing to the Integrated Primary Care Information (IPCI) database in 2000-2003. The IPCI database is a general practice research database which contains information from computer-based patient records of GPs in The Netherlands and is maintained by the Erasmus Medical Center.[28] The first practice was enrolled in the IPCI project in 1992 but a large proportion of practices started to contribute from 1998 onwards. In The Netherlands, GP records contain all relevant medical information on individual patients, since patients are registered to a single GP who has a gatekeeper role. To maximize completeness of the data, GPs who participate in the IPCI project are not allowed to use paper-based records. The computer-based records contain information on patient demographics, symptoms (free text), diagnosis (using the International Classification for Primary Care), referrals, laboratory measurements, and drug prescriptions (coded according to the Anatomic Therapeutic Chemical (ATC) classification system).[29;30] The database complies with European Union guidelines on the use of medical data for medical research, and has been proven valid using different reference methods for pharmaco-epidemiological research.[12;31] The Scientific and Ethical Advisory Group of the IPCI project approved the study.

Physician survey data

The GPs were asked to complete a questionnaire, designed to be short and easy to complete in order to optimize the response rate.[32] Major domains of the questionnaire included factors that may influence drug choice and the adoption of new drugs [18;33], i.e.: use of information sources, perceived benefits and risks of the drugs, the importance attached to specific drug characteristics, professional network, and general physician characteristics. The questionnaire items and format were pilot tested for clarity and face validity among eight GPs not related to the study population and revised accordingly.
GPs could first indicate how often they used various information sources in general (scientific medical journals, practice guidelines, national drug compendium, conferences/continuing education, formularies, computerized prescribing support system, pharmacotherapy counselling groups). Next, they were asked how often they would use various sources for

information on the treatment of hypertension on a scale from 1 (never) to 6 (always). Included were four professional sources (i.e. scientific medical journals, practice guidelines, national drug compendium, conferences/continuing education) and four commercial sources (i.e. pharmaceutical representatives, journal advertisements, direct mailings, sponsored meetings). Secondly, expectancies and values regarding different antihypertensive drug treatment aspects were measured. GPs were asked to grade their expectations regarding efficacy, user-friendliness of the dosage schedule, side effects and costs for each antihypertensive drug class on a scale from 1 (low on efficacy and user-friendliness; high on side effects and costs) to 10 (high on efficacy and user-friendliness; low on side effects and costs). This was used to calculate the perceived relative expectancy of ARBs in comparison to the average perceived expectancy of other antihypertensive drug classes (i.e. diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors (ACE inhibitors)). GPs were also asked to rate the importance of values attached to these aspects for their choice of antihypertensive treatment on a scale from 1 (not important) to 6 (important). Thirdly, GPs could indicate how often they perceived the influence of colleagues, hospital physicians and patients to prescribe new antihypertensive drugs on a scale from 1 (never) to 6 (always). Finally, GPs provided data on demographic details including age, gender, practice type (single-handed versus partnership), practice location (urban versus rural), practice size, workload, and work experience. GPs were also asked about their membership in professional societies, their involvement in developing guidelines, and their involvement in providing pharmacotherapy education. Most Dutch GPs participate in pharmacotherapy counselling groups that meet at least four times a year to exchange information and discuss pharmacotherapy. Not all GPs, however, are personally involved in preparing the content of these meetings. Additionally, GPs were asked about their participation in trials with antihypertensive drugs in the past five years. The initial survey mailing was made in May 2003. Telephone reminders and one follow-up mailing was made to non-respondents to encourage a high response rate.

Prescribing data for measuring adoption of ARBs

We were interested in the adoption of ARBs in routine prescribing. Therefore we looked at prevalent prescribing of ARBs to patients with hypertension in the year 2000 as indicator for adoption. This includes prescribing as initial or follow-up treatment, both monotherapy and combination therapy. To assess prevalent prescribing, we retrieved all prescriptions for antihypertensive drugs (diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, and ARBs) for patients with hypertension in a 6-months period before our index date (the first Wednesday in October 2000). This was roughly five years after the introduction of the first ARB on the Dutch market, and two years before the results of large clinical trials on cardiovascular endpoints on ARBs became available. Details on identification of these patients have been published elsewhere.[12] In brief, hypertension was identified from the medical records by a search on ICPC-code (K85, K86, and K87) and free text search on the diagnosis hypertension

followed by manual review. Data were also collected on presence of comorbidities and referrals to an internist or cardiologist.

Statistical analysis

Multivariable analyses were conducted to assess the influence of physician level determinants on prescribing ARBs rather than other antihypertensive drugs. These analyses were preceded by univariable analyses and data reduction procedures to reduce the number of independent variables. We assessed whether the use of professional and commercial information sources on hypertension treatment could be summated in two multi-item scales with acceptable reliability (Cronbach's alpha > 0.70).

Determinants of adoption were studied by linking physician related characteristics and views to their actual prescribing behaviour of ARBs, taking into account the possible effect of patient characteristics. Because of the hierarchy in the data, i.e. clustering of patients that receive care from the same GP, we used multilevel logistic regression with patient characteristics included at the first level and GP characteristics at the second level. All analyses were performed with MlwiN software, version 1.2. The multivariable multilevel models were built in two steps. First, we developed a multivariable model for all physician related variables, entering all variables that were significant at $P < 0.10$ level in the univariable analysis. All variables that remained significant at $P < 0.05$ level maintained into the final model (model 1). Second, we investigated the influence of physician related characteristics after adjustment for patient characteristics that could affect the probability of receiving ARBs, such as age, gender, presence of comorbidities, and referrals (model 2).[11;12] The influence of the variables on prescribing of ARBs is presented as odds ratios (OR) with 95% confidence intervals (CI).

Results

Study population

Seventy-two GPs completed the questionnaires (response rate: 96%). Two GPs who worked in partnership practices were excluded since they had less than 20 registered hypertensive patients. The final study population comprised 70 GPs and 9470 patients with hypertension who had received antihypertensive medication in the year 2000. These 70 GPs had a mean age of 49 years (SD 6), and were mainly male (84%). The majority worked full-time (65%), mostly in partnership practices and in urban areas. The mean size of practice was 2435 patients (SD 534). In this study, the percentage of males was slightly higher, the percentage of GPs working in urban areas was higher, and GPs were significantly older compared with the entire population of Dutch GPs. There were no substantial differences in terms of practice type and workload.

Of the 9470 patients treated for hypertension, 1093 patients were being prescribed ARBs (12%). There was a considerable variation in the use of ARBs between GPs (interquartile range, 6-15%). Thirty-two percent of the patients were treated with ACE inhibitors, 21% received calcium channel blockers, 41% beta-blockers, and 41% received diuretics. On average, patients received 1.5 antihypertensive drug prescriptions. Patients who were treated with ARBs were more likely than other hypertensive patients to be younger, to have asthma or chronic obstructive pulmonary disease, and were more likely to have been referred to an internist or cardiologist (**Table 1**).

Table 1 Characteristics of prevalent users of Angiotensin II receptor Blockers versus other antihypertensive drugs classes in 2000.

Characteristics	Angiotensin II Receptor Blocker Users (n=1093)	Users of other antihypertensive drug classes (n=8377)	*P* value
	Mean ± SD or number (%)		
Age (years)	64.2 ± 12.6	66.0 ± 12.9	< 0.001
Female	670 (61)	5189 (62)	0.691
Number of additional comorbidities	1.2 ± 1.3	1.2 ± 1.3	0.112
Angina pectoris	141 (13)	1108 (13)	0.812
Ankle oedema	119 (11)	977 (12)	0.482
Arrhythmia	136 (12)	879 (10)	0.054
Asthma / COPD	165 (15)	885 (11)	< 0.001
Diabetes	205 (19)	1472 (18)	0.333
Gout	62 (6)	493 (6)	0.837
Heart failure	60 (5)	539 (6)	0.261
Hypercholesterolemia	252 (23)	1764 (21)	0.135
Myocardial infarction	66 (6)	606 (7)	0.168
Proteinuria / renal insufficiency	29 (3)	243 (3)	0.701
Stroke	98 (9)	692 (8)	0.416
Referral to an internist	359 (33)	2288 (27)	< 0.001
Referral to a cardiologist	314 (29)	2031 (24)	0.002

COPD, chronic obstructive pulmonary disease.

Multi-item scales

The four-item scale on use of commercial information sources showed a high internal consistency (Cronbach's alpha = 0.77), and a summated score was therefore used for these commercial information sources. No multi-item scale could be identified for professional information sources because of lack of internal consistency (Cronbach's alpha < 0.7).

Table 2 Association between physician and patient characteristics and the physician's choice to prescribe Angiotensin II Receptor Blockers rather than other antihypertensive drug classes.

	Adjusted odds ratios (95% CI) Model 1*	Adjusted odds ratios (95% CI) Model 2	*N* (%)
Variables related to physicians			(n=70)
Commercial information sources			
Never/seldom	1	1	30 (43)
Average	1.23 (0.98-1.55)	1.25 (1.00-1.58)	31 (44)
Often/always	1.93 (1.48-2.52)	1.96 (1.51-2.56)	9 (13)
Use of a prescribing decision support system			
No	1	1	36 (52)
Yes	0.80 (0.66-0.97)	0.80 (0.66-0.97)	33 (48)
Personal involvement in pharmacotherapy education			
No	1	1	50 (72)
Yes	0.67 (0.51-0.88)	0.70 (0.53-0.92)	19 (28)
Perceived benefits on blood pressure reduction (per mark higher for ARBs vs. other drug classes)	1.17 (1.04-1.32)	1.19 (1.05-1.34)	-
Practice type			
Partnership	1	1	44 (63)
Single-handed	1.35 (1.10-1.65)	1.37 (1.12-1.69)	26 (37)
Practice location			
Urban	1	1	36 (51)
Rural	1.67 (1.33-2.10)	1.76 (1.40-2.22)	34 (49)
Variables related to patients			(n=9470)
Age (per year)		0.99 (0.98-0.99)	-
Asthma / COPD			
No		1	8420 (89)
Yes		1.51 (1.24-1.83)	1050 (11)
Myocardial Infarction			
No		1	8798 (93)
Yes		0.74 (0.55-1.00)	672 (7)
Referral to a cardiologist			
No		1	7125 (75)
Yes		1.41 (1.20-1.65)	2345 (25)
Referral to an internist			
No		1	6823 (72)
Yes		1.31 (1.13-1.51)	2647 (28)

* Multilevel logistic regression model representing probabilities of prescribing ARBs as odds ratios, with 95% confidence intervals. Model 1: model with all significant physician level variables ($P < 0.05$). Model 2: model with all significant physician level variables adjusted for patient characteristics. An odds ratio > 1 means a higher adoption level of ARBs. CI, confidence interval.

Determinants influencing adoption of ARBs

Multivariable analyses showed that adoption of ARBs was associated with various determinants on physician level (**Table 2**, model 1). Adjusting for patient characteristics did not change the effects of physician level variables (**Table 2**, model 2). ARB prescribing was positively associated with frequent use of commercial information sources (odds ratio [OR]=2.0; 95% confidence interval [CI] 1.5-2.6), but negatively associated with use of a computerized prescribing decision support system (OR=0.8; 95% CI 0.7-1.0). GPs involved in providing pharmacotherapy education were less inclined to prescribe ARBs (OR=0.7; 95% CI 0.5-0.9). Perceiving more benefits of ARBs in lowering blood pressure as compared to other antihypertensive drug classes was associated with higher adoption levels of ARBs. Finally, GPs who worked in single-handed practices or in rural areas were more likely to prescribe ARBs.

A number of factors appeared to be of little influence. No significant relation was observed between use of scientific medical journals, continuing education or other professional information sources and adoption of ARBs. GPs differed in the importance they assigned to specific drug characteristics, such as the importance of choosing a drug with high tolerability or low costs, but these differences in values were not related to differences in higher or lower adoption levels for ARBs. Also, participation in trials was not a significant factor. Furthermore, ARB prescribing was not higher among GPs who perceived more influence or pressure of hospital physicians and patients to prescribe newer antihypertensive drugs. Patients who were referred to an internist or cardiologist, however, were more likely to be treated with ARBs.

Discussion

Twelve percent of the hypertensive patients was treated with ARBs in 2000, showing a clear adoption of ARBs in routine prescribing. Marketing of pharmaceutical industries was the main explanatory variable for variation in adoption between GPs. The efforts put into implementing clinical guidelines and practicing evidence-based medicine have not altered this influence. Many of the other potential determinants could not explain the observed variation, indicating that the adoption of ARBs was not driven by a preference for ARBs based on a rational decision process nor by professional or patient pressures. Further adjustment for influences of specialist-initiated prescribing and relevant patient characteristics did not change these findings.

The Netherlands take an intermediate position regarding the adoption of ARBs, since ARB use for hypertension ranged from less than 5% in the UK to 20% in Norway in 2000.[34] It was hypothesized that the low adoption rate in the UK might be due to the efforts put into implementing evidence-based guidelines, whereas the high adoption rate in Norway might be the result of seeding trials.[34] Neither of these factors were the main driving forces for differences between adoption of ARBs within our country. We found that especially the use of

commercial information sources was related with higher adoption levels of this new drug class. Although many doctors acknowledge that the pharmaceutical industry tries to influence their prescribing, only few recognise themselves as being susceptible.[35] Physicians who prescribed more ARBs did have a more positive perception of their effectiveness in lowering blood pressure. However, this is not an evidence-based judgment.[9] Although we cannot determine a causal relationship, it is likely that promotional activities of the pharmaceutical industry played a role in the dissemination of these views. Pharmaceutical companies in the Netherlands devoted substantial resources to promote the advantages of ARBs in terms of efficacy and tolerability.[36] Overall, the amount of money spend on ARB promotion in the year 2000 was 1.4 times higher than on all other classes of antihypertensives together.[37]

The finding that GPs using a computerized prescribing decision support system have not adopted ARBs at a high rate is promising, but should be seen in the light that such systems were only just becoming available on a large scale at the time of our study. This implies that they could not have played an important role in the adoption process of ARBs in the period up to the year 2000. It is therefore not clear whether the use of decision support systems leads to better prescribing or doctors who are better prescribers in the first place are more likely to use decision support systems. Prescribing decision support systems can provide evidence-based recommendations to clinicians during the electronic prescribing process. There is some evidence that this can lead to more rational and less costly prescribing in primary care [38], but it has also become clear that these systems are used in variable frequency by GPs.[39;40] It is likely that especially GPs who already have a positive attitude towards evidence-based and cost-effective prescribing use these systems more frequently. This kind of attitude may also explain why personal involvement in providing pharmacotherapy education is associated with prescribing less ARBs. Cost-consciousness has been identified before as a relevant factor for restrictive prescribing of new drugs.[23;24]

Other studies showed that partnership practices adopted new drugs faster than single-handed practices, and suggested that continuous professional stimulation and other social factors might be a reason for this accelerated adoption.[15;41] We could not confirm this finding. On the contrary, adoption of new drugs was faster among physicians working in single-handed practices and in rural areas. This latter was also observed in a previous study.[16] Peer pressure was not found to be a driving force for the adoption of ARBs. There was, however, a clear effect of referrals to an internist or cardiologist on ARB treatment. Most GPs indicate that they usually continue prescriptions initiated by a hospital physician.

As an indicator for adoption we used prevalent prescribing of ARBs, since we aimed to identify determinants for the adoption of ARBs for routine use in hypertension treatment. In previous studies, we observed that the rapid increase in ARB prescribing shortly after their introduction in the market was not limited to specific patient groups or initial prescribing.[12;42] Dybdahl et al. (2004) demonstrated that most indicators of drug adoption correlate well with each other,

except for the indicator that focuses on time until the first prescription of a new drug.[17] The latter is not surprising since there is a clear difference between the decision to prescribe a new drug for the first time ever and adopting a drug into routine prescribing.

An important strength of our study is that we were able to link GP, practice and patient characteristics to actual prescribing patterns of ARBs. The IPCI project gave us the advantage to achieve a high response rate to our questionnaire survey combined with the complete access to prescribing data of their hypertensive patient population. Consequently, there was a little chance of information and selection bias. Although the percentage of older, male GPs working in urban areas that participated in our survey was slightly higher compared to the entire population of Dutch GPs, the trends in choice of antihypertensive treatment in the period 1996-2000 correspond with general trends in antihypertensive prescriptions in the Netherlands.[12;43;44] The database provided patient specific information which enabled us to correct for the possible effect of specialist-initiated prescribing and patient characteristics. A limitation of the study was that our survey was conducted in 2003, when the first studies on hard endpoints of ARBs had become available. This may have changed the perception of GPs regarding this aspect. We do not expect, however, that major changes occurred regarding the use of information sources, professional network, and general physician characteristics.

In summary, the adoption rate of a new drug class is still determined more by the physicians' reliance on promotional information than by their use of professional information sources. Our findings underline the continuous need to implement effective ways of dealing with the influence of the pharmaceutical industry rather than relying on promoting evidence-based medicine through traditional professional channels.

Acknowledgements

The authors are grateful to all GPs who participated in the IPCI project who completed the questionnaires, to S van 't Hooft-Lootens for her secretarial support in distributing the questionnaires, and to D de Zeeuw for his valuable comments on the manuscript. This study was supported by an unconditional research grant by Health Care Insurance Board, The Netherlands.

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Chapter 6

Claims in advertisements for Angiotensin II Receptor Blockers

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accepted for publication in J Hypert in revised form

Abstract

Objective

To determine how the pharmaceutical industry deals with evolving clinical evidence in their advertising claims for the different angiotensin II receptor blockers (ARBs) over a 9-year period, and whether a self-regulatory system is effective in ensuring that pharmaceutical promotion is up to standard.

Methods

We examined all advertisements from consecutive issues of the Dutch Journal of Medicine published between 1996-2004. We reviewed the content of advertisements for ARBs and judged whether claims were in agreement with the information available from the approved summary of product characteristics and evidence from cited clinical trials. Subsequently, we reviewed whether the claims had been assessed by the Code of Practice authority.

Results

We identified 28 unique advertisements with in total 290 appearances for seven ARBs. ARBs were the most frequently advertised antihypertensive drug class since 1998. Claims of blood pressure lowering, safety and convenient use were all judged to be sufficiently substantiated. Claims suggesting effects on long-term outcomes started in 1999, and were made in 13 unique advertisements. In 8 cases (56 appearances), claims suggesting protection or risk reduction were not supported by the available information. Some claims seemed to transfer results from a specific patient group to the general population of hypertensive patients. Two cases were reviewed by the Code of Practice authority.

Conclusions

One in every five advertisements for ARBs contained suggestive claims not supported by the information in the summary of product characteristics. The current system of self-regulation cannot ensure that pharmaceutical promotion is always accurate, balanced, and evidence-based.

Introduction

Concerns on the quality of drug advertising exist for many years. Several studies have documented inaccuracies and misleading claims in drug advertisements.[1-7] Individual countries have dealt with this problem in various ways. In Europe, the advertising of medicinal products was harmonised by the Council Directive 1992/28/EEC. In The Netherlands, this Directive was implemented in the form of the Medicinal Products Advertising Decree in 1994. Governments in Europe, Canada and Australia have ceded control of pharmaceutical promotion to Code of Practice authorities. These authorities have developed self-regulatory pharmaceutical advertising codes of conduct to which pharmaceutical companies are expected to adhere. According to these regulations, all claims concerning drugs should be accurate, up-to-date, truthful, correct, verifiable, and may not be misleading.[8;9] Advertising claims must not in any way conflict with the officially approved summary of product characteristics and must encourage rational drug use.[8]

Before a new drug is allowed on the market, it is tested in clinical trials to show its safety and efficacy, at least in terms of intermediate outcomes. This information is included in the summary of product characteristics, and can be used in advertising claims. Once on the market, new information may become available about side effects and long-term outcomes. In addition, new evidence on similar drugs belonging to the same drug class can become available. It is not clear how the pharmaceutical industry deals with this evolving clinical evidence in their advertising claims.

Up to now, studies on pharmaceutical advertising only documented the quality of claims in a particular year, and did not investigate how new research findings were presented in the advertisements over time.[3-7] Better insights in this process can help us identify whether current self-regulatory codes have been effective in ensuring that pharmaceutical promotion is up to standard.

We studied angiotensin II receptor blockers (ARBs) of which the first member was approved and introduced in 1995 and six additional class members became available within the next 8 years in The Netherlands. In 2001, it was shown for two ARBs that they decrease the progression of nephropathy in hypertensive patients with type 2 diabetes.[10-12] One year later, one ARB showed to reduce cardiovascular morbidity and mortality in hypertensive patients with left ventricular hypertrophy.[13]

We investigated trends in advertising claims for all ARBs over a 9-year period, determining whether claims were substantiated by scientific evidence in this period.

Methods

Data collection

We reviewed pharmaceutical advertisements appearing between 1 January 1996 and 31 December 2004 in the *Nederlands Tijdschrift voor Geneeskunde* (Dutch Journal of Medicine). This medical journal is published weekly and is among the most widely circulated medical journals in The Netherlands (circulation of 32,000 in 2004). Regarding advertisements for antihypertensive drugs we recorded brand names and therapeutic class (diuretics, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors [ACE inhibitors] and ARBs) in the 466 retrieved issues. Advertisements for ARBs which differed in text from other advertisements were defined as unique advertisements.

Advertisement classification

We reviewed the information content of each unique advertisement. We classified each promotional claim as stating or suggesting:

1. effects on intermediate outcomes (e.g. lowering blood pressure)
2. effects on long-term outcomes (e.g. effects beyond intermediate outcomes, including prevention or reduction of cardiovascular and/or renal disease or mortality, by using statements as 'effects on end-organs', 'protection' or 'risk reduction')
3. safety (e.g. excellent tolerability, placebo-like side effect profile)
4. convenience (e.g. low frequency of dosage, no drug interactions)
5. costs (e.g. low price, cost-effective)
6. new formulation
7. other indications than hypertension.

Next, we judged whether the claims were substantiated by cited clinical trials or information in the officially approved summary of product characteristics (**Table 1**). In our assessments, we followed the standpoint of the regulatory agencies, i.e. that positive effects on long-term outcomes can not be derived from proven efficacy on intermediate outcomes. All claims were evaluated independently by three reviewers. Individual classifications were compared, and in case of discrepancy, the advertisement was reviewed again and discussed until a consensus was reached. Claims were categorized as: supported by information in summary of product characteristics (SPC) or a cited clinical trial that was designed to assess this claim and published in a peer-reviewed journal (+); only supported by a cited trial that was either not yet published or not designed to assess this effect for this drug in hypertensive patients (~); or not supported by information in the SPC or a reference to a clinical trial (-). The first category represents claims that are considered sufficiently supported.

Table 1 Clinical trials cited in advertisements of angiotensin II receptor blockers.

Trial	Time	Treatment	Major findings
IDNT [11]	Sept, 2001	ARB vs. placebo CCB vs. placebo ARB vs. CCB	Irbesartan is effective in protecting against the progression of nephropathy due to type 2 diabetes, independent of the achieved reduction in blood pressure.
RENAAL [10]	Sept, 2001	ARB vs. placebo	Losartan conferred significant renal benefits in patients with type 2 diabetes and nephropathy, and it was generally well tolerated.
IRMA-2 [12]	Sept, 2001	ARB vs. placebo	Irbesartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 diabetes and microalbuminuria.
Val-HeFT [21]	Dec, 2001	ARB vs. placebo	Valsartan significantly reduced mortality and morbidity in patients with heart failure not treated with ACE inhibitors.
LIFE [13]	March, 2002	ARB vs. BB	Losartan prevents more cardiovascular morbidity and death than atenolol for similar reduction in blood pressure and is better tolerated.
VALUE [22]	June, 2004	ARB vs. CCB	No difference in morbidity and mortality between valsartan and amlodipine.

ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; BB, beta-blocker.

Subsequently, we examined whether the Code of Practice authority in The Netherlands had reviewed any of the advertising claims during the study period (CGR Foundation).[a]

Analyses

To assess trends, we calculated the proportion of advertisements for each antihypertensive drug class of all advertisements for antihypertensive drugs per year. To show the proportion of specific claims made for ARBs, we calculated the number of appearances of each type of claim divided by the total number of advertisements made for ARBs.

Results

Trends in advertisements

We identified a total of 492 advertisements for antihypertensive drugs during the period 1996-2004 in the Dutch Journal of Medicine. Of these, 290 (59%) were advertisements for ARBs. No advertisements for ARBs were observed in 1996, but ARBs have been the most frequently advertised antihypertensive drug class since 1998 (**Figure 1**).

Overall, 28 unique advertisements appeared for the seven ARBs. The ARBs each showed a different pattern of advertising both in quantity and timing. Some ARBs, e.g. irbesartan, candesartan, and eprosartan, were advertised continuously throughout the study period, whereas others, e.g. losartan, valsartan, and telmisartan, only for limited time periods (**Table 2**).

[a] Available at http://www.cgr.nl.

Table 2 Type of claims in 290 advertisements for seven different angiotensin II receptor blockers.

				Type of claim
Generic name*	Period	No. of ads appearances†	Trade name	Effects on blood pressure
Losartan	1995 – 1996	-	-	-
(March 1995)	1997	10	Hyzaar	
	1998 – 2000	-	-	-
	2001	12	Cozaar	X
	2001 – 2002	13	Cozaar	
	2002	4	Cozaar	
	2003 – 2004	-	-	-
Valsartan	1996 – 2001	-	-	-
(Nov 1996)	2002	2	(Co-)Diovan	X
	2003	-	-	-
	2004	6	(Co-)Diovan	X
	2004	1	(Co-)Diovan	X
	2004	5	Diovan	X
	2004	2	(Co-)Diovan	X
Irbesartan	1997 – 1998	18	Aprovel	X
(Aug 1997)	1998 – 1999	23	Aprovel	X
	1999 – 2000	23	(Co-)Aprovel	X
	2000 – 2001	17	(Co-)Aprovel	X
	2002	3	Aprovel	
	2002 – 2003	8	Aprovel	
	2004	4	(Co-)Aprovel	X
Candesartan	1997	-	-	-
(Oct 1997)	1998	18	Atacand	X
	1998 – 2000	32	Atacand	X
	2000 – 2001	12	Atacand	X
	2000 – 2001	11	Atacand (Plus)	X
	2002 – 2004	-	-	-
Eprosartan	1998 – 1999	-	-	-
(Jan 1998)	2000 – 2002	18	Teveten	
	2002 – 2003	6	Teveten	X
	2004	6	Teveten	X
Telmisartan	1999 – 2000	17	Micardis	X
(Dec 1998)	2001 – 2002	-	-	-
	2003	8	Micardis (Plus)	X
	2004	-	-	-
Olmesartan	2003	-	-	-
(May 2003)	2004	1	Olmetec	
	2004	5	Olmetec	X
	2004	5	Olmetec	X
Total ‡		290		233 (80)

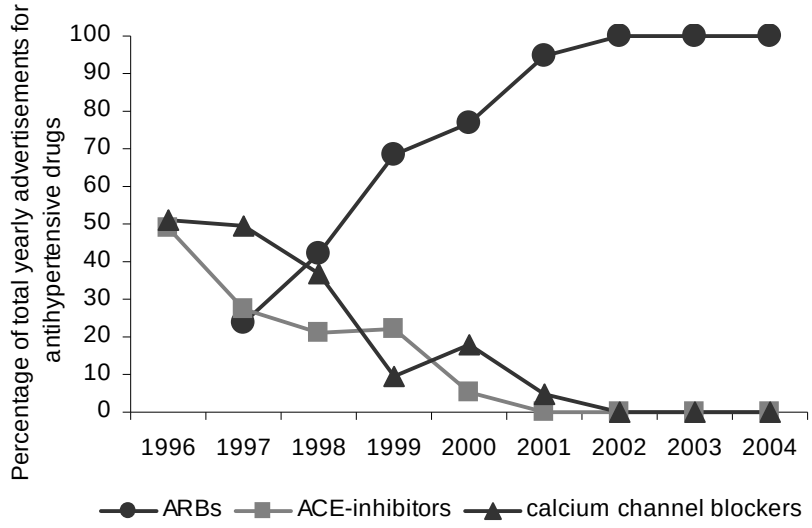
* In brackets is the date of regulatory approval in The Netherlands; † Number of times an advertisement with the same information content for the same trade name appeared;

Table 2 Continued

Type of claim				
Effects on long-term outcomes	Safety	Convenience	Costs	New formulation
-	-	-	-	-
	X			X
-	-	-	-	-
X	X	X		
X				
X	X			X
-	-	-	-	-
-	-	-	-	-
X				
-	-	-	-	-
X		X		
X				
X		X		
X		X		
	X			
	X			
	X			
X				
X				
X				
-	-	-	-	-
	X			
	X			
				X
-	-	-	-	-
-	-	-	-	-
		X	X	
X	X	X		
-	-	-	-	-
X		X		
-	-	-	-	-
-	-	-	-	-
				X
				X
				X
85 (29)	157 (54)	56 (19)	6 (2)	36 (12)

‡ Total number of advertisements for angiotensin II receptor blockers (proportion of advertisements with a certain type of claim).

Figure 1 Time trends in the proportion of the total number of advertisements for antihypertensive drugs devoted to different classes of antihypertensive drugs, 1996-2004.



ARB, angiotensin II receptor blocker

Trends in claims

During the whole study period, claims were made regarding efficacy in lowering blood pressure (**Table 2**). In total, 80% (233/290) of the advertisements for ARBs included such a claim. Claims suggesting effects on long-term outcomes started in 1999, and were made in 29% (85/290) of the advertisements. Approximately half (157/290) of the advertisements stated a claim of safety, but their frequency decreased dramatically by 2000. Some advertisements stated that ARBs were convenient in use (19%), mentioned new preparations (12%) or mentioned costs (2%).

Assessment of claims

Most claims were brief and non-specific. Claims regarding efficacy in lowering blood pressure, safety and convenient use were all judged to be sufficiently substantiated by the available information in the summary of product characteristics. Regarding safety, only vague claims were made like 'excellent tolerability' or 'placebo-like side effect profile'. None of the advertisements made specific claims, for instance, referring to the low incidence of side effects such as cough and angioedema or high persistence rates on ARBs.

Table 3 shows the 12 advertising claims made for four ARBs that we classified as stating or suggesting effects on long-term outcomes. These included four unique advertisements (appearing 28 times in total) that were considered to be sufficiently substantiated by the available evidence. For example, '25% more risk reduction for stroke (losartan)', 'renal protection and prevention in hypertensive patients with type 2 diabetes (irbesartan)' were substantiated by the cited trials. The claim '23% reduction of new-onset diabetes (valsartan)'

was supported by the VALUE trial but this was not a primary endpoint of this trial. In eight cases, claims were not substantiated by cited clinical trials or information in the summary of product characteristics. Advertisements with these claims appeared 57 times, which constituted 20% of all advertisements. For losartan, the first of a series of three unique advertisements with claims regarding effects on end-organs was considered premature. At that time, results from clinical trials showing long-term benefits were not yet published and the cited studies only showed effect on intermediate outcomes. In the first advertisement for valsartan, results on hard endpoints in heart failure patients were used in claims for an agent registered only for hypertension. In three subsequent advertisements, the claims 'valsartan protects' and 'a few millimetres reduction in blood pressure decrease gives kilometres cardiovascular protection' were made, again suggesting beneficial effects on morbidity or mortality in hypertensive patients for which there was no evidence provided. For irbesartan, the claim of long-term benefits was expanded to hypertensive patients in general in the last of a series of three unique advertisements. Finally, for telmisartan there were two advertisements appearing during 3 years in which the word 'protection in early morning hours' was used, partly in combination with a remark that this correlates with early morning cardiovascular events.

Complaints about promotional material

During the study period, the Code of Practice authority received complaints regarding two of the claims that we considered as being problematic. One of the complaints focussed on the claim 'significant reduction in mortality and morbidity, as proven in Val-HeFT' and another complaint was made for the claim 'valsartan protects'. The complainant alleged that claims using results from the Val-HeFT trial which consisted of heart failure patients suggested that heart failure was an approved indication for valsartan. The authority, however, did not rule on this complaint. Regarding the claim 'valsartan protects', the authority took the view that this was not in breach of the code since it was generally known that lowering blood pressure reduces the risk of end-organ damage. After this ruling in 2001, the complainant also felt free to make general claims of risk reduction for an ARB without further supporting evidence.

Table 3 Claims for angiotensin II receptor blockers suggesting or stating effects on long-term outcomes.

Product	Claim (literal translation)	Period	No. of ads appearances*	Support for this claim†	
Losartan	'favourable effects on end-organs'	February 2001 to October 2001	12 (1)	~	Cited clinical trials only showed effect on intermediate outcomes.
	'proven renal protection in hypertensive patients with type 2 diabetes and nephropathy'	October 2001 to May 2002	13 (1)	+	Cited RENAAL trial showed renoprotective effect of losartan in hypertensive patients with type 2 diabetes.
	'25% more risk reduction for stroke'	September 2002 to November 2002	4 (1)	+	Cited LIFE trial showed that losartan prevents more morbidity and death than atenolol in hypertensive patients.
Valsartan	'significant reduction in mortality and morbidity, as proven in Val-HeFT'	June 2002	2 (1)	~	Study population of the cited Val-HeFT trial consisted of heart failure patients, while heart failure was not an approved indication for valsartan.
	'valsartan protects'	January 2004 to April 2004	6 (1)	-	No cited trial or information in SPC showing beneficial effects of valsartan on mortality or morbidity in hypertensive patients.
	'23% reduction of new-onset diabetes'	July 2004	1 (1)	~	In the cited VALUE trial new-onset diabetes arose in fewer patients on valsartan than on amlodipine but this was not a primary endpoint of the trial.
	'a few millimetres reduction in blood pressure decrease gives kilometres cardiovascular protection'	July 2004 to October 2004	7 (2)	-	No cited trial or information in SPC showing beneficial effects of valsartan on mortality or morbidity in hypertensive patients.

Table 3 Continued

Product	Claim (literal translation)	Period	No. of ads appearances*	Support for this claim†	
Irbesartan	'renal protection and prevention in hypertensive patients with type 2 diabetes'	March 2002 to June 2002	3 (1)	+	Both the cited IDNT trial and IRMA-2 trial showed renoprotective effect of irbesartan in hypertensive patients with type 2 diabetes.
	'first ARB with an additional indication: treatment of nephropathy in hypertensive patients with type 2 diabetes'	September 2002 to November 2003	8 (1)	+	Based on results of the IDNT trial and IRMA-2 trial, irbesartan received the approval for this additional indication in SPC.
	'powerful authority in risk reduction, power over hypertension'	September 2004 to December 2004	4 (1)	-	No cited trial or information in SPC showing risk reduction of irbesartan in hypertensive patients in general.
Telmisartan	'protection in the early morning hours'	September 1999 to December 2000	17 (1)	~	The cited study assessed the antihypertensive effect and duration of action of telmisartan but not any protective effects. SPC states that beneficial effects of telmisartan on mortality and cardiovascular morbidity are currently unknown.
	'... offers protection against early morning peaks in blood pressure, which fall together with a peak incidence of cardiovascular events'	February 2003 to October 2003	8 (1)	~	The cited studies cited assessed the antihypertensive effect and duration of action of telmisartan, and did not show beneficial effects of telmisartan on cardiovascular events.

SPC, summary of product characteristics. * Number of times this advertisement with this claim appeared; number of unique advertisements in brackets. † Supported by information in SPC or a cited clinical trial that was designed to assess this effect (+), only supported by a cited trial that was either not yet published or not designed to assess this effect for this drug in hypertensive patients (~) or not supported by information in the SPC or a reference to a clinical trial (-).

Discussion

To our knowledge, this is the first study assessing the effects of evolving clinical evidence on pharmaceutical marketing claims in journal advertisements. We found that ARBs have been the most frequently advertised antihypertensive drug class in The Netherlands since 1998. While awaiting the results of large clinical trials, ARBs were mostly promoted using claims of their efficacy in lowering blood pressure and their excellent safety profile. These claims were all substantiated by information available at the time of regulatory approval.

Starting in 1999, claims suggesting efficacy beyond blood pressure lowering were observed, several of which were not supported by clinical trials or information in the summary of product characteristics. New information regarding good tolerability and high persistence rates on ARBs was not prominently used in the advertisements.

It is well-known that the pharmaceutical industry spends large amounts of money on promoting its products. This is particularly the case in a field in which several drugs compete for the same patient population, and pharmaceutical companies need to develop campaigns to distinguish between almost identical products. Under these circumstances, clinical research on long-term outcomes becomes part of a race to obtain results to strengthen the market position of a drug. Also in our study we observed advertisements with imprecise interpretation of scientific evidence. Just before the first results of trials on hard endpoints became available, losartan started to use the claim of beneficial effects on end-organs. Although with hindsight one could argue that this claim was correct, at that time it was not sufficiently substantiated. It has been shown that claims based on the results that have not yet been scrutinized and published in a peer-reviewed journal, can be overly optimistic.[14] Soon after the first trials on hard endpoints in hypertensive patients had been completed for some of the ARBs, advertisements for valsartan started to claim risk reduction using results from a trial evaluating effects in heart failure patients. It is not allowed to promote drugs for non-approved indications, and the advertisements indeed only mentioned the approved indication of hypertension. Advertisements for irbesartan showed that after a period of using claims clearly substantiated by clinical trials, also more general claims are made that are not based on such evidence.

Previous studies showed that the number of references to clinical trials in drug advertisements has increased in recent years, but many claims were still not adequately substantiated by these references.[5-7] These findings are troublesome, since research shows that drug advertising serves as an important source of information for physicians.[15;16] Although many physicians perceive themselves as paying little attention to drug advertisements, advertising has been shown to influence physicians' beliefs about the effectiveness of drugs.[15]

We defined general claims of 'protection' or 'risk reduction' as claims suggesting beneficial effects on long-term outcomes. This position was also taken by the Code of Practice authority

when they reviewed one of these claims but they did not object against using such a claim for a drug that had only proven to lower blood pressure. This differs from the standpoint of the regulatory agencies that we also used in our assessments, i.e. that positive effects on long-term outcomes can not be derived from proven efficacy on intermediate outcomes. After this ruling of the Code of Practice authority, another manufacturer also felt free to make general claims of risk reduction without further supporting evidence.

We assessed claims of 'placebo-like side effect profile' as adequately substantiated when the summary of product characteristics mentioned that the incidence pattern of side effects was comparable to a placebo. In the UK, however, complaints about claims of 'placebo-like tolerability' for both valsartan and irbesartan were reviewed in 2003 and 2004 by the Medicines and Healthcare products Regulatory Agency (MHRA).[b] This governmental agency, which is complimentary to the self-regulation by the pharmaceutical industry, considered this claim to be misleading as it implied that there were no drug associated side effects and suggested that the product was 'safer' than alternative medicines. In this respect the MHRA appears to take a different position than the self-regulatory Prescription Medicines Code of Practice Authority in the UK, which accepted that 'placebo-like tolerability' was a characteristic that could be attributed to various agents in the class of ARBs.[c]

Regulations and self-regulatory systems are probably effective in preventing some drug promotion abuses by providing the opportunity to submit complaints and by ruling against code violations.[6] Clear violations of specific requirements, such as referring to a clinical trial before it is published, were judged as breaching the Code of Practice. Rules on vague or suggestive claims are more difficult to make. Only two of the claims we considered as being problematic were reviewed by the Code of Practice authority. We do not know how many complaints were settled out of court.

These findings show the potential weaknesses of the current system. It has been suggested that there should be an active monitoring system for recognizing violations, independent monitoring committees, and effective sanctions for code violations.[3;7;17;18] The British example clearly shows that a governmental committee may be more critical in judging whether a claim might mislead the prescribers than a self-regulatory authority. Aside from a stricter control of the regulations, it has also been recommended to tighten them up.[19] Some specific requirements could be formulated to counter the observed problems. One could think of rules for mentioning the approved indication as well as the studied patient population on which claims are based clearly in the advertisement itself. Furthermore, a clear warning statement could be required in advertisements for drugs that have not yet proven efficacy on relevant

[b] The cases are in the section advertising complaints published on 2 April 2004 and 5 May 2004, available at http://www.mhra.gov.uk.

[c] The case is in the Code of practice Review, number 30, November 2000, available at http://www.abpi.org.uk/links/assoc/pmcpa.asp.

long-term outcomes. This would be on par with the European Medicines Agency guidelines from 1997 which state that the summary of product characteristics should explicitly mention when beneficial effects on mortality and cardiovascular morbidity are unknown until the results from adequate trials supporting this effect are available.[20] A strength of this study is that we collected data over a long time period enabling to assess the effects of evolving clinical evidence on marketing claims. During the study period, new evidence regarding efficacy and safety became available for the drug class studied.

There are some limitations. First, although we investigated all journal advertisements in the most widely circulated national medical journal, this may not reflect the frequency or types of claims in other medical journals nor in other types of promotion. Second, we assessed the textual content of the advertisements, whereas drugs are promoted through text as well as colourful, attention-grabbing images which can also inform and mislead the reader.[1]

In conclusion, this study showed that twenty percent of all ARB advertisements contained claims suggesting benefits that were not supported by the cited scientific evidence or the summary of product characteristics. Most of these claims were not reviewed by the self-regulatory authority. At this moment, physicians cannot fully rely on the current system of self-regulatory codes for pharmaceutical promotion. Before drawing conclusions from advertising claims, they need to investigate the supporting information themselves. An additional monitoring agency and tightened rules might help to ensure that pharmaceutical promotion is accurate, balanced, and evidence-based.

Acknowledgments

We have send this manuscript to Merck Sharpe & Dohme BV, Sanofi-Aventis BV, Boehringer Ingelheim BV and Novartis Pharma BV to offer them an opportunity to react on our results. They considered the criticised advertising claims to be legally correct according to the current codes and regulations, and felt supported in this by the rulings of the Code of Practice authority. Regarding telmisartan and losartan, our assessment that the claims suggested effects on long-term outcomes were disputed.

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Chapter 7

Physicians' attitudes towards treatment guidelines: differences between teaching and nonteaching hospitals

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European Journal of Clinical Pharmacology 2006; 62: 129-133

Abstract

Objective

To investigate whether physicians' attitudes towards treatment guidelines for primary and secondary care differ between teaching and nonteaching hospitals shortly before and 4 years after the guidelines' introduction.

Methods

Possible barriers and facilitators of joint treatment guidelines were obtained by self-administered questionnaires twice during the study period. Questionnaires were distributed among all internists and cardiologists in the Groningen region of The Netherlands.

Results

Physicians from teaching and nonteaching hospitals differed in attitude regarding the content and usefulness of the guidelines. Physicians from nonteaching hospitals more often believed that the guidelines are too restrictive (64% vs. 18%) and too rigid to apply to individual patients (14% vs. 6%), and that they oversimplify medical practice (79% vs. 35%). Physicians from teaching hospitals more often agreed that good recommendations for first-choice drugs had been made (76% vs. 50%) and that these guidelines are a convenient source of advice (94% vs. 57%), can facilitate communication with general practitioners (94% vs. 71%), and can improve the quality of pharmacotherapeutic care (88% vs. 43%). Four years later, a larger proportion of physicians from both hospital settings had a negative attitude towards the usefulness of the guidelines, but the difference in attitude between teaching and nonteaching hospitals remained the same.

Conclusion

Physicians from nonteaching hospitals were less positive about the usefulness of joint treatment guidelines than physicians from teaching hospitals were. Results from studies on the implementation of guidelines in teaching hospitals can therefore not be transferred to nonteaching settings.

Introduction

Treatment guidelines have evolved greatly in the past 20 years and are regarded as the cornerstone in improved health quality and medical cost control. However, their implementation has proved to be difficult.[1;2] Understanding physicians' attitudes towards guidelines may be helpful in creating strategies to successfully implement them.

In the year 2000, several programmes were set up in The Netherlands to improve the quality and consistency of therapeutic care between primary and secondary care. The approach chosen in several regions was to develop joint treatment guidelines to be used both by hospital physicians and general practitioners (GPs). In Groningen, a region in the north of The Netherlands, new guidelines were developed by local committees of hospital physicians, GPs, and community and hospital pharmacists. They used available evidence as well as existing national guidelines and local formularies for either primary or secondary care to establish these joint treatment guidelines. Drugs of first choice were chosen for all relevant indications and subpopulations.

Previous research showed that hospital physicians expressed both positive and negative attitudes towards the regional joint treatment guidelines.[3] Other studies found that most hospital physicians have a positive attitude towards guidelines in general, perceiving them to be of educational value and likely to improve quality of care.[4-7] However, physicians also expressed concerns that guidelines were too rigid to apply to individual patients and that they reduced physician autonomy.[4;5;7] Physicians' attitudes may differ between settings because of differences in organisational culture and patient populations.[8-10] Little is known about differences in physicians' attitudes across hospital settings. We investigated whether physicians' attitudes towards regional joint treatment guidelines differed between teaching and nonteaching hospitals shortly before the guidelines' introduction and 4 years later.

Methods

Setting

As part of a larger study evaluating the usefulness of cardiovascular treatment guidelines, we surveyed all general internists and cardiologists in the Groningen region. This region includes five hospitals, 260 GPs, and 570,000 inhabitants. One hospital is a large university hospital where physicians are employed by the hospital. The second is a large teaching hospital where physicians work in private group practices. The remaining three hospitals are nonteaching hospitals where physicians also work in private group practices.

Guideline development and implementation

The first version of the joint treatment guidelines covered 16 therapeutic indications for different specialties. For most of the included topics, local or national guidelines already existed but were intended primarily for either GPs or specialists. The newly developed guidelines were unique by combining recommendations for both professional groups, thereby streamlining treatment choices across the primary-secondary care interface. The first version of the guidelines was distributed to all health care providers by mail in 2001. In 2004, the guidelines were updated and expanded to cover 43 topics. They were again distributed by mail.
During the first 4 years, the local institute for rational drug use developed a few implementation projects for GPs, but no specific programme was developed to implement the joint treatment guidelines in the hospitals. Hospital physicians received only a general newsletter about the regional project twice a year.

Data collection

Possible differences in barriers and facilitators of joint treatment guidelines between teaching and nonteaching hospitals were obtained by self-administered questionnaires twice during the study period. The first questionnaire was given to all 36 general internists and 24 cardiologists working in the Groningen region at the end of 2000, shortly before the introduction of the joint treatment guidelines. In the second survey, the group of internists was expanded with the subspecialties endocrinology and nephrology to a total number of 54, and the number of cardiologists working in the region had increased to 36. The second questionnaire was mailed to all these internists and cardiologists in the autumn of 2004, after the updated version of the guidelines had become available. A single reminder letter and a second copy of the questionnaire were sent to nonrespondents 3 weeks later.
Questionnaires were developed using statements from existing instruments, such as the Attitudes Towards Guidelines Scale [11], and were supplemented by statements derived from previous qualitative research among hospital physicians.[12] The first questionnaire included 34 statements of possible barriers and facilitators of joint treatment guidelines that covered four domains: content of the guidelines (eight items), development process of the guidelines (four items), usefulness and value (15 items), and aspects of organisation and setting (seven items).[3] The follow-up questionnaire included statements about physicians' perceived usefulness and value of the guidelines on which physicians differed at the time of the introduction (eight items). Attitudes about guidelines were assessed using 7-point ordinal scales, with 1 indicating "strongly agree" and 7 indicating "strongly disagree". The 7-point ordinal scales were collapsed into categories of agreement (response 1-3), neutral (response 4), and disagreement (responses 5-7).

Data analysis

Differences in demographic characteristics between physicians from teaching and nonteaching hospitals and between participants and the regional physician population were tested with chi-square tests. Chi-square tests were also used to determine differences in survey responses between physicians from the two teaching hospitals and three nonteaching hospitals and to assess possible differences in attitudes between early and late respondents and between respondents on the first and second surveys.

Results

First survey

Thirty-one physicians, 15 general internists and 16 cardiologists, completed the questionnaires during the first survey (response rate 52%). The mean and standard deviation of age was 47 ± 7 years; two physicians (6%) were women; and 17 (55%) were working in teaching hospitals. This was not significantly different from the entire group of cardiologists and internists in the Groningen region at that time in terms of gender or percentage of physicians working in teaching hospitals. There were also no significant differences between physicians from teaching and nonteaching hospitals with respect to age, gender, or specialty.

Physicians from teaching and nonteaching hospitals differed in attitude regarding two of the eight items dealing with the guidelines' content and six of the 15 items focusing on the usefulness and value of the guidelines. More physicians from nonteaching hospitals compared with those from teaching hospitals considered the guidelines to be too restrictive and did not agree with the recommendations made for first-choice drugs (**Table 1**). Physicians from nonteaching hospitals more often believed that the guidelines were too rigid to apply to individual patients and that they oversimplified medical practice. In addition, physicians from nonteaching hospitals agreed less often that these guidelines could facilitate communication with GPs or could improve the quality of pharmacotherapeutic care. Almost half of the physicians from teaching hospitals and more than two-thirds of the physicians from nonteaching hospitals perceived no need for using the guidelines. Physicians from nonteaching hospitals also seemed to have more reservations regarding the organisational aspects of implementing these guidelines, but none of these differences were statistically significant. Most physicians agreed that the guidelines were developed by experts (93%), useful as an educational tool (87%), well-applicable in practice (74%), and likely to improve harmonisation between primary and secondary care (90%). Physicians from teaching hospitals in particular agreed that the guidelines were a convenient source of advice. At the same time, many physicians expressed concerns about misuse of these guidelines by government and insurance companies (74%) and negative influence of guidelines on innovation (61%).

Table 1 Percentages of hospital physicians who agreed and disagreed with statements about joint treatment guidelines in 2000

	Physicians in teaching hospitals (n=17)		Physicians in nonteaching hospitals (n=14)		Chi² test* (df=2)
	Agree	Disagree	Agree	Disagree	
Guideline content					
These guidelines are based on scientific evidence	94	6	86	0	
These guidelines recommend what I already do in practice	88	6	93	0	
Within drug classes good choices have been made in these guidelines	76	24	50	14	*P* = 0.03
These guidelines are outdated	24	59	43	36	
These guidelines are too restrictive	18	71	64	21	*P* = 0.02
These guidelines are too conservative	18	71	36	43	
Too many equivalent drugs are included in these guidelines	6	82	7	71	
These guidelines should have given recommendations on drug class level only	35	59	75	25	
Guideline development process					
The people in the developing committees are appropriate representatives of my professional group	63	19	71	14	
These guidelines are developed by experts	94	0	93	7	
The guideline development initiative is dominated too much by financial interests	50	19	79	0	
The distance between the developers of these guidelines and practitioners is too big	44	19	50	14	
Usefulness and value of guidelines					
These guidelines are useful as an educational tool	94	0	79	21	
These guidelines are a convenient source of advice	94	0	57	29	*P* = 0.03
These guidelines can facilitate communication with general practitioners	94	0	71	29	*P* = 0.05
These guidelines can facilitate communication with patients and families	59	24	43	43	
These guidelines can improve the quality of pharmacotherapeutic care	88	0	43	21	*P* = 0.02
These guidelines can lead to better harmony between primary and secondary care	88	6	92	8	
These guidelines can lead to cost savings	59	12	57	29	
These guidelines are well-applicable in practice	88	0	57	14	
These guidelines facilitate taking over patients from colleagues	59	24	50	36	
These guidelines can be misused by government and insurance companies	59	18	93	7	
These guidelines limit innovation	47	47	79	21	
I do not need these guidelines	47	41	71	21	
These guidelines challenge my professional autonomy	19	69	79	14	*P* < 0.01

Table 1 Continued

	Physicians in teaching hospitals (n=17)		Physicians in nonteaching hospitals (n=14)		Chi² test* (df=2)
	Agree	Disagree	Agree	Disagree	
Usefulness and value of guidelines (continued)					
These guideline oversimplify medical practice	35	47	79	14	*P* = 0.05
Many of my patients cannot be treated according to these guidelines	6	88	14	43	*P* = 0.03
Organisation and setting					
Most of my colleagues have disapproving attitudes about these guidelines	18	65	29	36	
These guidelines are not valued in my practice organisation	12	59	21	21	
Implementing these guidelines is too time-consuming and expensive	12	65	50	36	
With these guidelines I lose industry support for conducting research	35	65	36	57	
With these guidelines I lose industry support for conferences and educational meetings	24	65	50	43	
Some of my patients do not want to be treated according to these guidelines	18	65	54	38	
These guidelines thwart local guidelines and agreements	0	76	21	64	

* Comparing numbers of specialists and general practitioners agreeing, disagreeing, or having a neutral opinion; only *P* values ≤ 0.05 are reported.

Many physicians reported that the guideline development initiative was dominated too much by financial interests (63%).

Second survey

Of the 90 physicians surveyed 4 years after the introduction of the regional joint treatment guidelines, 50 (56%) responded to the survey, 32 internists and 18 cardiologists. Participating physicians had a mean age of 47 ± 8 years; six (12%) were women; and 38 (76%) were working in teaching hospitals. This was representative for the entire group of cardiologists and internists in the Groningen region at that time in terms of gender and percentage of physicians working in teaching hospitals.

Overall, a larger proportion of physicians from both hospital settings had a negative attitude towards usefulness and value of the guidelines at the second survey, but the differences in attitudes between teaching and nonteaching hospitals remained similar (**Table 2**). Comparing the first and the second surveys as independent samples, significantly more negative attitudes were observed for three of the eight statements (chi-square tests, *P* < 0.05).

Table 2 Percentages of hospitals physicians who agreed and disagreed with statements about joint treatment guidelines in 2004

	Physicians in teaching hospitals (n=38)		Physicians in nonteaching hospitals (n=12)		Chi² test* (df=2)
	Agree	Disagree	Agree	Disagree	
Usefulness and value of guidelines					
These guidelines are a convenient source of advice	66	11	50	25	
These guidelines can facilitate communication with general practitioners	76	5	33	25	*P* = 0.02
These guidelines can improve quality of pharmacotherapeutic care	61	8	27	45	*P* = 0.01
These guidelines are well-applicable in practice	37	16	17	33	
These guidelines limit innovation	45	39	67	0	*P* = 0.03
These guidelines challenge my professional autonomy	37	39	83	0	*P* = 0.01
Many of my patients cannot be treated according to these guidelines	26	29	58	0	*P* = 0.04
These guidelines oversimplify medical practice	47	29	83	8	

* Comparing numbers of specialists and general practitioners agreeing, disagreeing, or having a neutral opinion; only *P* values ≤ 0.05 are reported

Late respondent analysis

On average, 40% of the late respondents (n=11) and 26% of the early respondents (n=39) expressed neutral responses. Early respondents had more positive as well as more negative attitudes than late respondents. Overall, there was no significant difference in attitudes between the early and the late respondents (chi-square test, $P > 0.05$). In addition, respondents and nonrespondents did not differ in terms of gender, specialty, or percentage working in teaching hospitals.

Discussion

We found that physicians from nonteaching hospitals viewed the regional joint treatment guidelines less favourably than did physicians from teaching hospitals. Four years after the guidelines' introduction, more physicians from both settings expressed a negative attitude towards the usefulness of these guidelines, while the difference between teaching and nonteaching hospitals remained the same.

We evaluated the attitudes towards these guidelines without being involved in their development or implementation. This independent status may have been an important factor for retrieving candid answers from the respondents. Treatment guidelines were perceived as a burden and a source of irritation by many hospital physicians, particularly in nonteaching

hospitals. Despite the fact that the physicians felt adequately represented in the committees that developed the guidelines and believed that the guidelines were based on scientific evidence, they were not content with the idea of being faced with the guidelines themselves. Important beliefs underlying this discontent are that (1) specialists believe they already make good drug choices and do not need guidelines telling them what to do in their fields of expertise, and (2) guidelines restrict the choice of drugs to save costs for the government and insurance companies but may lead to loss of industry support for research and conferences. Dependence on industry sponsorship for education and research can make physicians unwilling to divert from certain brand preferences.[13]

Physicians from teaching hospitals were more positive than those from nonteaching hospitals. Explanations may lie in differences in utility of the guidelines, patient populations, economic and organisational consequences, and cultural differences.[8-10] Utility of the guidelines appears to be a relevant factor in our study. In teaching hospitals, physicians can use the guidelines in their educational activities; therefore, they see more benefits of having the guidelines. Surprisingly, physicians from nonteaching hospitals expected more problems regarding their patient population than physicians from teaching hospitals did. This is in contrast with an earlier finding that especially in teaching hospitals one could expect difficulties with treating complex patients according to guideline recommendations.[12] Strong physician leadership advocating guideline use may be an important factor.[13] In teaching hospitals, one can expect a stronger culture to promote the use of evidence-based guidelines. Results from an Italian survey suggested that there may also be economic and organisational reasons for differences in attitudes towards guidelines, but our study does not support this finding.[4] Physicians from private and non-private practices represented within our two teaching hospitals showed similar attitudes. Teaching status appears to be a more important factor than being employed by the hospital or not.

Our study provided insight into the changing attitude towards usefulness of treatment guidelines over time. The finding that physicians became more negative has been observed before, and it has been suggested that physicians' attitudes may change as they perceive that guidelines are being used more for cost containment than for quality improvement.[6] This was clearly an issue of discussion in our region, since the guidelines have been used in 2002 in negotiations to make cost agreements with the industry. Another factor that might have influenced changes in attitude over time is the lack of a specific implementation programme. The joint treatment guidelines in our study were distributed by mail, and such passive dissemination has been shown to be largely ineffective.[13] Supporting strategies to implement treatment guidelines soon after their introduction may be crucial. To motivate physicians to start using the guidelines at present, an intensive implementation strategy will be needed.

Our study has some limitations. Using a questionnaire is an efficient way to examine attitudes and barriers, but socially desirable answers may form a problem. We have tried to limit this by

using positive as well as negative statements and by emphasising that the data would be processed anonymously. Furthermore, the generalisation of our findings is somewhat limited because we studied a modest number of physicians in each hospital setting, and not all physicians participated in both surveys. Although we achieved response rates above 50%, response bias may affect the results. We observed that early respondents expressed more pronounced attitudes compared with physicians who responded after the reminder and, possibly, with the remaining nonrespondents. However, the early respondents had both more positive and more negative attitudes. Therefore, we do not expect our results to be skewed due to response bias, for instance towards the more discontented physicians. There were also no substantial differences between respondents and nonrespondents with respect to gender, specialty, or percentage of physicians working in teaching hospitals.

In conclusion, physicians' attitudes towards treatment guidelines differ between teaching and nonteaching hospitals. Up to now, most research focussing on the implementation of treatment guidelines has been performed in teaching hospitals. Considering the findings of our study, results from such studies cannot be transferred to nonteaching settings. One might expect more difficulties when treatment guidelines are implemented in a nonteaching hospital setting.

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Chapter 8

Summary and General Discussion

Although the efficacy and safety of antihypertensive and lipid-lowering drugs have been extensively established in clinical trials and results from such trials have been incorporated into evidence-based practice guidelines, antihypertensive and lipid-lowering drugs appear not to be prescribed at optimal rates in daily medical practice. This thesis presents a series of studies exploring trends in cardiovascular drug prescribing in Dutch general practice. We have focussed on whether antihypertensive drugs, in particular ACE inhibitors and ARBs, and lipid-lowering drugs were prescribed appropriately and according to the guideline recommendations on hypertension and hyperlipidemia. We studied the influence of patient-related and physician-related factors on (new) cardiovascular drug prescribing. In the previous chapters, each specific study was described in detail, including the shortcomings and merits. In this final chapter, the most important findings are summarized and some methodological considerations are discussed. In addition, implications of this research for physicians, policymakers and future research are discussed.

Main findings

Patterns of cardiovascular drug prescribing and patient-related factors

The first part of this thesis focussed on patterns of antihypertensive and lipid-lowering drug prescribing in Dutch general practice and the influence of patient-related factors. Trends in choice of antihypertensive drug classes were assessed in **chapter 2**. This study was conducted in a cohort of hypertensive patients who were identified from the Integrated Primary Care Information (IPCI) database in the Netherlands. Between 1996 and 2000, prevalence of antihypertensive drug use increased steadily in hypertensive patients (from 68% to 73%). Also, the average number of antihypertensives prescribed per patient increased (from 1.4 to 1.5). Time trends showed that there was a significant increase in prevalent use of beta-blockers (from 38% to 43%) and ARBs (from 2% to 11%), whereas prevalent use of calcium channel blockers somewhat decreased (from 22% to 21%), and prevalent use of diuretics (41%) and ACE inhibitors (31%) remained stable over the years. While prevalent use of ACE inhibitors had stabilized, we observed an increased use of ACE inhibitors (from 33% to 41%) in patients for whom such drugs were recommended, i.e. hypertensive patients who also have heart failure, diabetes mellitus, proteinuria and/or renal insufficiency. By contrast, trends in prescribing of ARBs were not in agreement with evidence-based guidelines at that time. ARB use significantly increased immediately after its introduction in hypertensive patients with and without specific comorbidities. In addition, ARBs were used while benefits on cardiovascular morbidity and mortality were still uncertain and sufficient evidence-based alternatives were available.

In **chapter 3** we assessed whether the start of ARB use during the period 1996-2000 was in agreement with the recommendations of Dutch guidelines for hypertension. ARBs were only

recommended as alternative for patients who do not tolerate ACE inhibitors. The objective of this study was to examine trends in prescribing of ARBs as initial and second-line treatment of hypertension. Prescribing data for 3.102 newly treated hypertensive patients were extracted from the Integrated Primary Care Information database. During the period 1996-1999, initial ARB use increased significantly from 4% to 10%. The use of ARBs as second-line treatment was much lower. ARBs were used as second-line treatment in less than 4% of all hypertensive patients who were initially treated with an antihypertensive drug other than an ARB: 2% switched to an ARB (mostly from ACE inhibitors) and 1% received ARBs as add-on treatment. From this study, we can conclude that ARBs have achieved a position in the treatment of hypertension as initial rather than second-line therapy which was not in accordance with guideline recommendations for hypertension that were effective during this study period.

Trends in initiating and intensifying antihypertensive and lipid-lowering therapy in the period 1998-2004 in type 2 diabetes patients were investigated in **chapter 4**. Information on drug prescribing and on cardiovascular risk factors was obtained from the Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC)-study in The Netherlands. In this project, general practitioners were supported by hospital-based diabetes specialist nurses for the annual control of approximately 2.400 type 2 diabetes patients. We observed an overall increased use of antihypertensive and lipid-lowering drug therapies and better control of risk factors between 1998 and 2004. The percentage of hypertensive patients decreased only slightly (≥ 150/85mmHg; from 58% to 51%), whereas the percentage of patients with elevated TC/HDL ratio (> 6) decreased considerably (from 29% to 4%). The proportion of type 2 diabetes patients initiated on antihypertensive therapy increased (from 20% to 29%), as did the percentage of intensifications in patients already on antihypertensive therapy (from 19% to 35%). However, still two-third of patients with insufficiently controlled blood pressure in 2003 did not receive an initiation or intensification of antihypertensive treatment. The proportion of patients who were initiated on lipid-lowering therapy increased substantially (from 12% to 35%), whereas intensification of lipid-lowering therapy remained low (12% in 1999 vs. 7% in 2004). The number of patients with insufficiently controlled lipid levels was already quite low by the year 2004, leaving not much room for further improvement in this group of patients. Among patients with both elevated blood pressure and lipid levels, and therefore at increased risk of cardiovascular disease, we did not observe higher initiation rates for lipid-lowering therapy. The decision to increase pharmacological treatment was influenced by the level of the risk factor itself, but not by the presence of other risk factors.

Physician-level factors related to cardiovascular drug prescribing

The second part of this thesis focussed on physician-level factors relevant for understanding the dynamics of cardiovascular drug prescribing. Special attention was given to physician-level

factors related to the adoption of ARBs, since we aimed to explore possible reasons for variation in ARB prescribing among Dutch general practitioners.
To gain insight into possible reasons underlying the rapid increase in prescribing of ARBs observed in **chapters 2** and **3**, we linked physician-related characteristics to their actual prescribing behaviour in **chapter 5**. A questionnaire was completed by 70 general practitioners (GPs) contributing data to the Integrated Primary Care Information (IPCI) database (response rate: 96%). This questionnaire consisted of the following domains comprising factors that may influence drug choice and the adoption of new drugs, i.e.: use of information sources, perceived benefits and risks of different antihypertensive drug classes, the importance attached to specific drug characteristics, professional network, and general physician characteristics. Prescribing data of antihypertensive drugs were obtained from the Integrated Primary Care Information database. GPs who reported frequent use of commercial information sources were more likely to prescribe ARBs routinely in preference to other antihypertensives, whereas GPs who used a prescribing decision support system and those who were involved in pharmacotherapy education were somewhat less likely to prescribe ARBs. Other factors that were associated with higher levels of ARB adoption included a more positive perception of ARBs regarding their effectiveness in lowering blood pressure, and working in single-handed practices or in rural areas. Many of the other potential determinants could not explain the observed variation in ARB prescribing, indicating that the adoption of ARBs was not driven by a preference for ARBs based on a rational decision process nor by influence of hospital physicians nor by pressure from patients.

Interactions between pharmaceutical industries and physicians are inevitable but not always undesirable. At market introduction an information asymmetry about the new drug's clinical profile exists between the drug company and health care providers. The drug companies have been collecting information about the drug's efficacy and safety for years through extensive clinical testing, while the drug is rather unknown to physicians. Once on the market, new information may become available about side effects and long-term outcomes. Drug companies use this information in their marketing campaigns to inform physicians about their products. In **chapter 6**, we evaluated how the pharmaceutical industry dealt with evolving clinical evidence in their advertising claims for the different ARBs. We identified a total of 290 advertisements for ARBs during the period 1996-2004 in the *Nederlands Tijdschrift voor Geneeskunde* (Dutch Journal of Medicine). While awaiting the results of large clinical trials, ARBs were mostly promoted using claims of their efficacy in lowering blood pressure and their excellent safety profile. These claims were all substantiated by clinical evidence already available at the time of regulatory approval. Starting in 1999, claims suggesting beneficial effects on long-term outcomes were observed in 12 different advertisements, most using general statements as 'favourable effects on end-organs', 'protection' or 'risk reduction'. In eight cases (57 appearances), these claims were not supported by the information in the

summary of product characteristics or evidence from a cited clinical trial. In some cases these claims were not supported by any reference at all, in other cases the drug was recommended in a patient group other than that assessed in the cited trial. The self-regulatory Code of Practice authority received complaints regarding two of these claims only. These findings are troublesome, since research shows that drug advertising serves as an important source of information for physicians.[1;2]

In **chapter 7**, we investigated whether specialists' attitudes towards cardiovascular joint treatment guidelines for primary and secondary care differed between hospitals. A questionnaire was completed by 31 general internists and cardiologists in the Groningen region of The Netherlands (response rate: 52%). In general, physicians from nonteaching hospitals (n=14) viewed the joint treatment guidelines less favourably than did physicians from teaching hospitals (n=17). Physicians from nonteaching hospitals more often believed that the guidelines are too restrictive (64% vs. 18%) and too rigid to apply to individual patients (14% vs. 6%) and that they oversimplify medical practice (79% vs. 35%). Physicians from teaching hospitals more often agreed that good recommendations for first-choice drugs had been made (76% vs. 50%) and that these guidelines are a convenient source of advice (94% vs. 57%), can facilitate communication with general practitioners (94% vs. 71%), and can improve the quality of pharmacotherapeutic care (88% vs. 43%).

Methodological considerations using general practice databases for drug research

General practice data

This thesis describes several studies exploring trends in cardiovascular drug prescribing in Dutch general practice. Most of these studies used data from the Integrated Primary Care Information (IPCI) database in the Netherlands. The IPCI database is a longitudinal observational general practice research database containing the complete electronic medical records from approximately 200.000 patients. We used the IPCI database to explore trends in antihypertensive drug prescribing for the following reasons. Firstly, we had access to a large population of hypertensive patients that were followed over time. Secondly, as the IPCI database contains the complete electronic medical records, information on patient demographics, diagnosis, comorbidity, and drug prescriptions can be retrieved. In addition, the IPCI project gave us the opportunity to collect additional information on physician-related factors that may influence drug choice and the adoption of new drugs. Therefore, we were able to link physician-related factors to their actual prescribing behaviour to identify determinants for adoption of ARBs in routine prescribing for hypertension.

Data from the ZODIAC-study were used to investigate trends in initiating and intensifying antihypertensive and lipid-lowering therapy. An important strength of this study is that we had access to a large population of type 2 diabetes patients that were followed over time. Secondly, this study provided information on medical history (including year of onset diabetes and history of myocardial infarction and/or angina pectoris), measurements of blood pressure and weight, and laboratory findings (i.e.: HbA1c, total cholesterol, HDL cholesterol, and LDL cholesterol), besides data on patient demographics and drug prescriptions. Therefore, we were able to study which patient factors influence general practitioners to prescribe antihypertensive and lipid lowering drugs in a routine practice setting.

Internal and external validity

The validity, or the degree to which a finding is likely to be true, is very important. Commonly, two aspects of validity are considered namely the internal and external validity.

The internal validity of a study refers to the integrity of the study design, i.e. the ability to measure what is set out to be measured. In observational studies there is always a potential for selection bias, information bias and confounding, which undermines the internal validity of epidemiological research.

An important form of selection bias is referral bias where patients voluntary refer themselves to take part in epidemiological research. As the IPCI database encompasses the total patient population and the data are gathered prospectively, without knowledge of the later formulated research questions, the magnitude of selection bias is negligible. With regard to the type 2 diabetes patients in the ZODIAC-study, working groups of physicians participated with their type 2 diabetes population in the study as a whole.[3] Although patients themselves had to give their informed consent and had to visit the diabetes specialist nurse yearly, patient participation rate remained high throughout the study period (90% of the patients responded to the invitation for a consultation with the diabetes specialist nurse at least twice during the first three years).[3] It is possible that patients who volunteered for yearly screening are generally more health-conscious than those who did not volunteer. Another possibility is that some of the patients who volunteered for screening may have volunteered because they were especially worried about their health. These biases counteract one another, but because neither one is easy to quantify, the net selection bias is unknown.

Information bias, also known as misclassification bias, measurement bias or recall bias, results from an incorrect determination of exposure or outcome. This information bias might be random (non-differential) or systematic (differential). Non-differential misclassification almost always results in an underestimate of the true strength of the relationship, whereas differential misclassification may result in overestimation as well as underestimation of the

actual risk. In general, information bias is a much smaller problem in routinely collected patient data compared with interview and questionnaire data. Data on patients' demographics, diagnosis, comorbidity and referrals was gathered from the IPCI database independently of prescribing data for antihypertensive drugs. We might have underestimated actual prescribing rates, since we used prescribing data from a general practice research database that did not include specialists' prescriptions. With regard to risk factor levels, it may happen that laboratory results are more likely to be documented in patients with insufficiently controlled risk factor levels than in well-controlled patients. This bias was mainly avoided in the ZODIAC-study since diabetes specialists' nurses used standardized report forms to document annual control findings. We might have underestimated actual prescribing rates, since our outcome assessment was mainly based on patient reported use of drugs.
Overall, we may have misclassified some of the exposure and outcome measurements. However, it is likely that exposure and outcome misclassification was mainly non-differential and therefore the reported association estimates are an underestimate of the true risk.

Confounding is one of the major concerns in epidemiologic research, as it is one of the most difficult biases to detect and control for. Confounding can lead to an overestimation or underestimation of the true association between exposure and outcome. We mostly applied multivariable techniques (e.g. mathematical modelling via multivariable logistic regression analysis or proportional hazard analysis) to control for confounding.

External validity of epidemiologic research implies that the observed findings can be generalized to the general population. As we used data from the IPCI database, a large general practice research database, we believe that our results regarding the choice of antihypertensive treatment can be extrapolated to the general population of hypertensive adults. Furthermore, trends in the choice of antihypertensive treatment in the period from 1996 to 2000 corresponded with the general trends in antihypertensive prescriptions in The Netherlands.[4;5] Results from the ZODIAC-study on trends in initiating and intensifying antihypertensive and lipid-lowering therapy should be seen in the light that these improvements were achieved within a shared-care project. Hospital-based diabetes specialist nurses, who performed the annual control of type 2 diabetes patients, may have facilitated physicians to provide better care.[3] The findings of this study may therefore reflect a best-case scenario and cannot simply be extrapolated to the management of hypertension and hyperlipidemia in Dutch general practice in general.

Undertreatment of hypertension and hyperlipidemia

Although the use of antihypertensive and lipid-lowering drug therapies has increased in the past decade, undertreatment of hypertension and hyperlipidemia is still present (**chapters 2** and **4**). We observed that about two-third of type 2 diabetes patients eligible for the

pharmacological treatment of hypertension in 2004 was either untreated or was uncontrolled. Physicians did not increase lipid-lowering drug therapy adequately for patients with both uncontrolled blood pressure and lipid levels. Suboptimal management of hypertension or hyperlipidemia is especially alarming in type 2 diabetes patients. Type 2 diabetes patients have high rates of hypertension and hyperlipidemia, contributing to the two- to four-fold increased risk of cardiovascular disease.[6]

Several causes have been proposed why physicians may not initiate or intensify therapy appropriately. It has been ascribed to clinical inertia – recognition of the problem of hypertension and hyperlipidemia, but failure to act.[7] Proposed explanations for clinical inertia include physicians' overestimation of their adherence to guidelines, or acceptance of elevated risk factors in their patients, lack of training on achieving therapeutic goals, possible lack of motivation to treat asymptomatic conditions, pharmacotherapy pill burden, and time limitations.[7-9] Barriers related to carrying out cardiovascular risk assessment have also been reported. Physicians were not used to risk estimation, and physicians had more confidence in their own clinical judgement than risk tables or charts.[10] Barriers relating to the content and format of the risk tables were also present.[11] Furthermore, physicians were confused by the lack of agreement with other (inter)national risk guidelines.[11] Many different Dutch practice guidelines existed for hyperlipidemia, hypertension and type 2 diabetes, and as a result various guideline recommendations for the prevention of cardiovascular disease were given. By the year 2003, it was realized that effective cardiovascular risk management would require more agreement between guideline recommendations. This led to the development of an integrated cardiovascular risk management guideline.[12] This recently published guideline is already an important step forward. It may reduce the lack of consistency and can provide better support for health care providers.

Adoption of new drugs

According to the guideline recommendations for hypertension regarding first-choice antihypertensive drug classes in 2000, ARBs should have been prescribed only in patients unable to tolerate ACE inhibitors. However, ARBs achieved a marked position as initial treatment for hypertension in the period 1996-2000. Moreover, this position was not restricted to patients with relevant comorbidities (**chapters 2** and **3**). Thus, ARBs were already used as initial treatment in uncomplicated hypertensive patients before trials on cardiovascular endpoints became available. A different picture emerged regarding the prescribing of ACE inhibitors. Prescribing of ACE inhibitors seems to have developed into a pattern that is more in accordance with guideline recommendations, since increases in the use of ACE inhibitors were only observed in patients for whom these drugs were recommended. Differences in prescribing patterns between ACE inhibitors and ARBs suggest that increases in use of new drugs shortly

after their introduction are largely not specific but, in later years, become more confined to patients for whom this is more evidence-based.

Marketing of pharmaceutical industries is the main explanatory variable for the rapid adoption of new drugs as reported in **chapter 5** and repeatedly shown by others.[1;13-15] Pharmaceutical companies succeeded in launching ARBs in the market as 'ACE inhibitors without cough' instead of a new class of antihypertensive drugs.[16] ACE inhibitors were already proven useful in the treatment of hypertension, the treatment of heart failure, and the prevention of renal failure progression.[17-20] Furthermore, studies showing that ARBs were better tolerated and had higher persistence rates than other antihypertensive drug classes probably encouraged prescribing of ARBs as the initial treatment.[21-24]

However, many patients may have been exposed to uncertain risks during the early post-marketing period of ARBs. Use of new drugs in daily medical practice can, and often does, unveil unknown effects that were not detected during clinical testing before market approval. New drugs are approved on the basis of studies of usually limited duration, relatively small numbers of patients, using strict inclusion criteria resulting in a study population far different from patients in daily medical practice. There is still a high degree of uncertainty at the moment of market introduction about the new drugs' effectiveness and safety profile when used in large populations. Although newer drugs are nowadays relatively safe when they receive market authorisation, several new drugs (for example, mibefradil, cerivastatin and rofecoxib) were withdrawn after being on the market for only a few years. This advocates restraint in prescribing during the early post-marketing period.

Implications

Treatment of hypertension and hyperlipidemia has improved in the past decade but is still far from optimal. Many type 2 diabetes patients with hypertension remained untreated and many treated patients did not achieve target levels of these risk factors. Moreover, the increase in pharmacological treatment was only influenced by the level of the risk factor itself, but not by the presence of other risk factors. Programs or strategies to improve treatment of these important cardiovascular risk factors are needed because risk factors continue to contribute to disease progression and impaired prognosis. In addition, drug choices have been shifted to newer and less extensively evaluated drugs.

Traditional approaches to improve uptake of research findings have focused on better availability and presentation of evidence by identifying, synthesising, and disseminating evidence to doctors in practical accessible formats (e.g. clinical guidelines, reviews in medical journals, and better access to electronic sources of information). Although this approach may be all that is needed to ensure the uptake of some simple changes, most changes in practice

require further efforts. Adherence to guidelines may be hindered by a variety of barriers, such as method of development used, content of the recommendations, source of dissemination and implementation.[25-27] One promising approach to implement evidence-based medicine into routine general practice are educational interventions, such as continuing medical education courses and pharmacotherapy peer review groups (in Dutch called FTO) that set goals about optimising pharmacotherapy and audit prescribing.[28;29] However, not all educational programs have direct impact on improving prescribing practice.[30] Interventions on implementing evidence-based medicine may not be generalizable, since barriers in one setting may not be present in another.[25;31] Other interventions to achieve optimal management of cardiovascular risk factors include disease management, educational outreach visits, and computerized reminder systems.[32-35] Also, providing information to patients about risk factors and medical treatment recommendations may be effective for initiating and maintaining therapy.[36]

The problem of overprescribing with newer and less extensively evaluated drugs should be further addressed at the level of policy and education. Marketing of pharmaceutical industries is still the main explanatory variable for the adoption of new drugs.[15;37] Although many doctors acknowledge that the pharmaceutical industry tries to influence their prescribing, only few recognise themselves as being susceptible.[38] Thus, educational programmes aiming at a better understanding and analysis of pharmaceutical promotion strategies are certainly needed. In addition, professional organisations should try to provide objective, scientific information to physicians soon after the introduction of a new drug. In line with marketing campaigns that are completely tuned to special features of a new drug, educational programs to influence new drug prescribing need to be tailored to every new drug individually. Furthermore, there should be a stricter control of the self-regulatory system for pharmaceutical drug promotion. Regulations and self-regulatory systems are probably effective in preventing some drug promotion abuses by providing the opportunity to submit complaints and by ruling against code violations.[39] However, there should be an active monitoring system for recognizing violations, independent monitoring committees, and effective sanctions for code violations.[40-43] Aside from a stricter control of the regulations, it has also been recommended to tighten them up.[44] Some specific requirements could be formulated to counter the observed problem of vague, suggestive claims. One could think of rules for mentioning the approved indication as well as the studied patient population on which claims are based clearly in pharmaceutical promotional materials. Furthermore, a clear warning statement could be required for drugs that have not yet proven efficacy on relevant long-term outcomes. This would be on par with the European Medicines Agency guidelines from 1997 which state that the summary of product characteristics should explicitly mention when beneficial effects on mortality and cardiovascular morbidity are unknown until the results from adequate trials supporting this effect are available.[45]

We noted that only a small group of physicians seemed to be accountable for the early adoption of ARBs, as found in earlier studies as well.[15;46-49] From these studies it has become clear that prescribing new drugs was very much dependent on the new drug in question and not so much on the prescriber. Physicians who rapidly adopt one new drug do not necessarily adopt other new drugs quickly. This lack of predictability has important implications for policy makers who would like to control prescribing of new drugs. The interaction between the new drug and the physician needs to be analysed and used as starting point before developing any policy to ensure optimal use of new drugs.

Final considerations

The studies describes in this thesis provide sufficient opportunities for interventions aiming at the improvement of pharmacotherapy of hypertension and hyperlipidemia, including initiating and intensifying cardiovascular drugs to improve attainment of treatment goals, targeting cardiovascular drugs to those benefiting most from them, and prescribing newer antihypertensive drug classes when necessary. Ongoing monitoring and measurement of the quality of care, empowering physicians with medical decision-support tools and evidence-based information about new drugs are essential to improve uptake of research findings in routine general practice.

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Nederlandse samenvatting

Hoewel de effectiviteit en veiligheid van antihypertensiva en lipidenverlagende geneesmiddelen uitgebreid in klinische studies is vastgesteld en in behandelingsrichtlijnen is opgenomen, blijken deze geneesmiddelen niet altijd optimaal in de dagelijkse huisartsenpraktijk te worden voorgeschreven. Dit proefschrift omvat een serie onderzoeken naar trends in het voorschrijven van cardiovasculaire geneesmiddelen in de Nederlandse huisartsenpraktijk. Dit proefschrift concentreert zich op de vraag in hoeverre het voorschrijven van antihypertensiva, in het bijzonder ACE-remmers en angiotensine-II-antagonisten, en lipidenverlagende geneesmiddelen in het afgelopen decennium volgens de behandelingsrichtlijnen voor hoge bloeddruk en cholesterol is verlopen. Daarnaast is de invloed van patiënt- en artsgerelateerde factoren op het voorschrijven van (nieuwe) cardiovasculaire geneesmiddelen bestudeerd.

Trends in het voorschrijven van cardiovasculaire geneesmidden en patiëntgerelateerde factoren

Het eerste deel van dit proefschrift richt zich op trends in het voorschrijven van antihypertensiva en lipidenverlagende geneesmiddelen in de Nederlandse huisartsenpraktijk en de invloed van patiëntgerelateerde factoren. Trends in het voorschrijven van de verschillende klassen antihypertensiva werden beoordeeld in **hoofdstuk 2**. Deze studie werd uitgevoerd in een cohort hypertensiepatiënten afkomstig uit de 'Integrated Primary Care Information' (IPCI) database van het Erasmus MC uit Rotterdam. De IPCI database is een longitudinaal elektronisch huisartsenbestand van ongeveer 200.000 patiënten. Tussen 1996 en 2000 steeg het gebruik van antihypertensiva onder patiënten met een te hoge bloeddruk gestaag (van 68% naar 73%). Daarnaast steeg ook het gemiddelde aantal geneesmiddelen dat aan deze patiënten tegen een te hoge bloeddruk werd voorgeschreven van 1.4 naar 1.5. De trends over de tijd lieten een significante toename in het gebruik van bètablokkers (van 38% tot 43%) en angiotensine-II-antagonisten zien (van 2% tot 11%), terwijl het gebruik van calciumantagonisten enigszins verminderde (van 22% tot 21%) en het gebruik van diuretica (41%) en ACE-remmers (31%) stabiel bleef. Terwijl het gebruik van ACE-remmers in zijn totaliteit stabiel bleef, observeerden we een toename in het gebruik van ACE-remmers (van 33% tot 41%) in patiënten voor wie deze geneesmiddelen worden aanbevolen, d.w.z. patiënten met een te hoge bloeddruk die hartfalen, diabetes mellitus en/of proteïnurie en/of nierinsufficiëntie hebben. Dit in tegenstelling tot de trends in het voorschrijven van angiotensine-II-antagonisten die niet in overeenstemming waren met behandelingsrichtlijnen uit die periode. Het gebruik van angiotensine-II-antagonisten steeg vrijwel onmiddellijk na de marktintroductie bij patiënten met te hoge bloeddruk met en zonder specifieke comorbiditeiten, terwijl angiotensine-II-antagonisten alleen geadviseerd werden als alternatief voor patiënten die een ACE-remmer niet konden verdragen. Bovendien werden angiotensine-II-antagonisten voorgeschreven terwijl de voordelen op cardiovasculaire morbiditeit en

mortaliteit nog onzeker waren en er voldoende alternatieven met bewezen effectiviteit beschikbaar waren.

In **hoofdstuk 3** werden de voorschrijfpatronen van angiotensine-II-antagonisten gedurende de periode 1996-2000 nader onder de loep genomen. Het doel van deze studie was om trends in het voorschrijven van angiotensine-II-antagonisten als eerste keus en tweede keus behandeling te beschrijven. We bestudeerden de voorschrijfgegevens van 3.102 nieuw behandelde hypertensiepatiënten afkomstig uit de IPCI database. In de periode 1996-1999 steeg het gebruik van angiotensine-II-antagonisten als startbehandeling van 4% naar 10%. Het gebruik van angiotensine-II-antagonisten als tweede keus geneesmiddel was veel lager. Angiotensine-II-antagonisten werden gebruikt als tweede keus geneesmiddel in minder dan 4% van alle hypertensiepatiënten die al eerder een ander geneesmiddel tegen hoge bloeddruk als monotherapie gehad hadden: 2% kreeg een angiotensine-II-antagonist als monotherapie (voornamelijk patiënten die eerst een ACE-remmer hadden gehad) en 1% kreeg een angiotensine-II-antagonist als combinatietherapie. Uit deze studie kunnen we concluderen dat angiotensine-II-antagonisten eerder een positie hebben bereikt in de initiële behandeling dan in de tweede keus behandeling. Dit is niet in overeenstemming met de behandelingsrichtlijnen voor hoge bloeddruk die tijdens de studieperiode van kracht waren.

Trends in het starten en intensiveren van de behandeling met antihypertensiva of lipidenverlagende geneesmiddelen voor patiënten met diabetes type 2 in de periode 1998-2004 zijn onderzocht in **hoofdstuk 4**. Informatie over het voorschrijven van geneesmiddelen en over cardiovasculaire risicofactoren werd verkregen uit de Zwolle Outpatient Diabetes project Integrated Available Care (ZODIAC)-studie. In dit project krijgen de deelnemende huisartsen ondersteuning van de diabetesverpleegkundigen bij de jaarlijkse controle van al hun ongeveer 2400 type 2 diabetespatiënten. We observeerden een toename in het gebruik van antihypertensiva en lipidenverlagende geneesmiddelen en een betere controle van risicofactoren over de jaren 1998-2004. Het percentage patiënten met een te hoge bloeddruk (≥ 150/85 mmHg) daalde lichtelijk van 58% naar 51%, terwijl het percentage patiënten met een verhoogd totaal cholesterol/HDL ratio (>6) aanzienlijk verminderde (van 29% naar 4%). Het percentage type 2 patiënten dat voor het eerst een geneesmiddel tegen hoge bloeddruk kreeg voorgeschreven nam toe (van 20% naar 29%), evenals het percentage patiënten dat een intensivering van hun behandeling tegen hoge bloeddruk kreeg (van 19% naar 35%). Tweederde van de patiënten met een te hoge bloeddruk in 2003 kreeg echter geen antihypertensivum voorgeschreven of kreeg geen intensivering van hun bestaande behandeling. Het percentage patiënten dat met een lipidenverlagende geneesmiddel startte nam aanzienlijk toe (van 12% naar 35%), terwijl het intensiveren van de lipidenverlagende behandeling laag bleef (12% in 1999 versus 7% in 2004). Het aantal patiënten met een

verstoord lipidenspectrum was al behoorlijk laag in 2004, zodat niet veel ruimte voor verdere verbetering van deze groep patiënten overbleef. Onder patiënten met zowel een verhoogde bloeddruk als een verstoord lipidenspectrum, en daardoor een verhoogd cardiovasculair risico, vonden we geen verhoogd percentage lipidenverlagende startbehandelingen. Het besluit om medicatie te starten of te verhogen werd beïnvloed door het niveau van de bijbehorende risicofactor en niet door de aanwezigheid van andere risicofactoren.

Artskenmerken gerelateerd aan het voorschrijven van cardiovasculaire geneesmiddelen.

In het tweede deel van dit proefschrift ligt de focus op artskenmerken die relevant kunnen zijn voor het begrijpen van de variatie in het voorschrijven van cardiovasculaire geneesmiddelen. Speciale aandacht werd gegeven aan artskenmerken gerelateerd aan de adoptie van angiotensine-II-antagonisten, omdat we op zoek waren naar mogelijke redenen die de variatie in het voorschrijven van angiotensine-II-antagonisten tussen Nederlandse huisartsen kunnen verklaren. Om inzicht te krijgen in de onderliggende redenen van de snelle stijging in het voorschrijven van angiotensine-II-antagonisten, zoals beschreven in **hoofdstuk 2** en **3**, hebben we artskenmerken gekoppeld aan hun daadwerkelijke voorschrijfgedrag (**hoofdstuk 5**). Een vragenlijst werd ingevuld door 70 huisartsen die data leverden aan de IPCI database (respons: 96%). De vragenlijst bestond uit verschillende onderdelen, die mogelijk de geneesmiddelenkeuze en de adoptie van nieuwe geneesmiddelen kunnen beïnvloeden: gebruik van informatiebronnen, de waargenomen voor- en nadelen van de verschillende klassen antihypertensiva, het belang gehecht aan specifieke geneesmiddelenkenmerken, professioneel netwerk en algemene artskenmerken. Voorschrijfgegevens van antihypertensiva zijn verkregen uit de IPCI database. Huisartsen die een hoog gebruik van commerciële informatiebronnen rapporteerden, bleken vaker angiotensine-II-antagonisten dan andere antihypertensiva voor te schrijven. Huisartsen die een elektronisch voorschrijfsysteem gebruikten en huisartsen die betrokken waren bij farmacotherapie onderwijs, bleken iets minder angiotensine-II-antagonisten voor te schrijven. Andere factoren gerelateerd aan het voorschrijven van angiotensine-II-antagonisten waren een positievere perceptie van angiotensine-II-antagonisten ten aanzien van hun effectiviteit in het verlagen van de bloeddruk, het werkzaam zijn in een solopraktijk of in minder stedelijk gebied. Veel van de andere potentiële factoren konden niet de waargenomen variatie in het voorschrijven van angiotensine-II-antagonisten verklaren. Dit wijst erop dat het voorschrijven van angiotensine-II-antagonisten niet werd bepaald door een voorkeur voor angiotensine-II-antagonisten gebaseerd op rationele overwegingen, noch door de invloed van specialisten of door druk van patiënten.

Interacties tussen de farmaceutische industrie en artsen zijn onvermijdelijk maar niet altijd ongewenst. Bij de marktintroductie van een nieuw geneesmiddel bestaat er een informatie

asymmetrie over het klinische profiel van een nieuw geneesmiddel tussen de geneesmiddelenfabrikanten en artsen. De geneesmiddelenfabrikanten hebben jarenlang uitgebreide klinische testen uitgevoerd om informatie over de effectiviteit en veiligheid van het geneesmiddel te verzamelen, terwijl het geneesmiddel bij artsen vrijwel onbekend is. Wanneer een geneesmiddel eenmaal op de markt is, kan nieuwe informatie over bijwerkingen en lange termijneffecten beschikbaar komen. Geneesmiddelenfabrikanten gebruiken deze informatie in hun marketingcampagnes om artsen over hun producten te informeren. In **hoofdstuk 6** evalueerden we hoe de farmaceutische industrie omgaat met steeds verder ontwikkelend klinisch bewijs in hun advertentieclaims voor de verschillende angiotensine-II-antagonisten. We bestudeerden in totaal 290 advertenties voor angiotensine-II-antagonisten in het Nederlands Tijdschrift voor Geneeskunde gedurende de periode 1996-2004. Terwijl de resultaten van grote klinische trials werden afgewacht, werden angiotensine-II-antagonisten aan de man gebracht met claims over effectiviteit in het verlagen van de bloeddruk met daarbij een gunstig bijwerkingenprofiel. Deze claims werden allen voldoende onderbouwd met klinisch bewijsmateriaal dat al beschikbaar was op het tijdstip van registratie van het geneesmiddel op de Nederlandse markt. Vanaf 1999 werden claims die gunstige effecten op lange termijneindpunten suggereerden geobserveerd in 12 verschillende advertenties. De meeste advertenties gebruikten algemene beweringen zoals ‘gunstig effect op eindorganen’, ‘bescherming’ of ‘risicoreductie’. In acht gevallen (57 verschijningen) werden deze beweringen niet ondersteund door de informatie in de 1B-tekst (= de wetenschappelijke productinformatie van een geneesmiddel) of met een verwijzing naar bewijsmateriaal van een klinische studie. In sommige gevallen werden deze beweringen helemaal niet ondersteund met referenties, in andere gevallen werd het geneesmiddel geadviseerd in een patiëntengroep anders dan beoordeeld was in de aangehaalde studie. Het zelfregelende toezicht door de Stichting Code Geneesmiddelenreclame ontving slechts twee klachten naar aanleiding van deze beweringen. Deze bevindingen geven aanleiding tot zorg, gezien het belang van geneesmiddelenreclame als bron van informatie voor artsen.

Aangezien het voorschrijven van cardiovasculaire geneesmiddelen door huisartsen veelal het resultaat is van herhalingen van voorschriften van geneesmiddelen die geïnitieerd zijn door specialisten, onderzochten we in **hoofdstuk 7** of de houdingen van specialisten ten opzichte van transmurale cardiovasculaire behandelingsrichtlijnen tussen de ziekenhuizen verschilden. Een vragenlijst werd ingevuld door 31 algemene internisten en cardiologen in de provincie Groningen (respons: 52%). Over het algemeen waren de specialisten uit de perifere ziekenhuizen (n=14) minder positief over de behandelingsrichtlijnen dan specialisten uit de opleidingsziekenhuizen (n=17). De specialisten uit de perifere ziekenhuizen waren vaker van mening dat de richtlijnen te restrictief zijn (64% versus 18%), te beperkend om op individuele patiënten van toepassing te zijn (14% versus 6%) en dat zij de medische praktijk te eenvoudig

voorstellen (79% versus 35%). De specialisten uit de opleidingsziekenhuizen waren het er vaker mee eens dat goede aanbevelingen voor eerste keus geneesmiddelen waren gedaan (76% versus 50%), de richtlijnen een geschikte bron voor advies zijn (94% versus 57%), de richtlijnen de communicatie met huisartsen kan vergemakkelijken (94% versus 71%) en de kwaliteit van farmacotherapeutische zorg kan verbeteren (88% versus 43%).

Tenslotte worden in **hoofdstuk 8** de belangrijkste resultaten en conclusies van het proefschrift samengevat en verschillende methodologische aspecten bediscussieerd. Bovendien worden de bevindingen uit de gepresenteerde studies besproken in het licht van de primaire doelstelling van dit proefschrift en worden de implicaties van het onderzoek besproken, namelijk in hoeverre het voorschrijven van antihypertensiva en lipidenverlagende geneesmiddelen in het afgelopen decennium volgens de behandelingsrichtlijnen is verlopen. Concluderend kan gesteld worden dat de behandeling van de cardiovasculaire risicofactoren hypertensie en hyperlipidemie sterk verbeterd is, maar nog niet optimaal is. Patiënten met meerdere risicofactoren kunnen bijvoorbeeld nog intensiever met medicatie behandeld worden. Nieuwere geneesmiddelen, zoals de angiotensine-II-antagonisten, zouden terughoudender moeten worden voorgeschreven in de periode waarin lange termijn effecten nog niet bekend zijn en er voldoende alternatieven aanwezig zijn. Regelmatig geactualiseerde behandelingsrichtlijnen en wetenschappelijke informatie over nieuwe geneesmiddelen zijn belangrijk om de kwaliteit van het voorschrijven van cardiovasculaire geneesmiddelen in de dagelijkse huisartsenpraktijk te bevorderen.

Dankwoord

Op het moment dat ik dit schrijf is mijn proefschrift bijna af. Een goed moment om een heel aantal mensen te bedanken waarmee ik samen tot dit eindresultaat ben gekomen. Ik hoop maar dat ik niemand vergeet...

Promotoren en co-promotor

Allereerst wil ik mijn beide promotoren, prof dr FM Haaijer-Ruskamp en prof dr D de Zeeuw, bedanken. Beste Floor, ik kan me nog goed mijn sollicitatiegesprek herinneren, waarin je me vroeg of ik ook wilde promoveren. Toen vond ik een onderzoeksproject van twee jaar eerst wel lang genoeg en kon ook nog niet vermoeden dat ik vier jaar later met de laatste loodjes van mijn proefschrift bezig zou zijn. Ik wil je bedanken voor je inspirerende en plezierige samenwerking. Je was betrokken bij het onderzoek maar gaf ook ruimte en vertrouwen, dat heb ik erg in je gewaardeerd.

Beste Dick, van een afstandje was je zeer betrokken en vooral je klinische blik en kennis op het gebied van de angiotensine-2 antagonisten heeft erg bijgedragen aan de kwaliteit van dit proefschrift, dank hiervoor. Ik wil je bedanken voor je verfrissende kijk op mijn manuscripten, je enthousiasme als er weer een artikel geaccepteerd was en natuurlijk voor de mogelijkheid dat ik dit onderzoek op jouw afdeling mocht uitvoeren.

Een speciaal woord van dank aan mijn co-promotor, dr P Denig. Beste Petra, mijn dank is groot. Ik heb ontzettend veel van je geleerd, zeker wat betreft het uitvoeren van onderzoek op het gebied van rationeel geneesmiddelengebruik, maar ook wat betreft het schrijven van wetenschappelijke artikelen. De nauwgezette manier waarop jij ieder manuscript van commentaar voorzag om ze vooral leesbaarder te maken en de opbouwende manier waarop jij altijd feedback gaf, zijn voor mij steeds een stimulans geweest om verder te gaan. Petra, een kritischer en meer betrokken co-promotor kan je je als promovendus niet wensen!

Co-auteurs

Vele co-auteurs hebben een bijdrage geleverd aan de verschillende hoofdstukken in dit proefschrift. Graag wil ik dr WJ van der Veen en dr FW Beltman bedanken voor de prettige leerzame samenwerking tijdens de eerste twee jaren. Willem Jan, dank voor het bewaken van de methodologische kant van het onderzoek en de hulp bij het uitvoeren van de analyses. Frank, bedankt voor het delen van jouw expertise op het gebied van de behandeling van hoge bloeddruk in de huisartspraktijk. Daarnaast wil ik dr MCJM Sturkenboom bedanken voor de mogelijkheid om onderzoek te doen met gegevens uit de IPCI database. Miriam en ook Jeanne Dieleman, bedankt voor jullie hulp bij de selectie van de hypertensiepatiënten. Ik heb heel wat weken op de 'IPCI kamer' in Rotterdam moeten doorbrengen, maar uiteindelijk heeft dat een prachtige dataset met patiëntengegevens opgeleverd. Dr HJG Bilo wil ik bedanken voor de mogelijkheid om gebruik te maken van gegevens uit het Zwolse diabetesproject. In dit kader verdienen ook alle artsen en patiënten een vermelding in dit dankwoord, zij hebben een enorme schat aan gegevens geleverd. Dank ook aan Sylvia van 't Hooft-Lootens voor de

administratieve ondersteuning bij het vragenlijstonderzoek onder de IPCI artsen, Jana Rampelmann voor het doorspitten van ruim 450 uitgaven van het Nederlands Tijdschrift voor Geneeskunde, Gert Broekhaar voor het aanleveren van de Zwolse data, Lielith Ubink-Veltmaat en Anneke Stegeman voor alle uitleg bij de dataverzameling van het Zwolse diabetesproject.

Leescommissie

Graag wil ik ook de leescommissie, prof dr PA de Graeff, prof dr LTW de Jong-van den Berg en prof dr K van der Meer, bedanken voor de tijd die jullie genomen hebben voor de beoordeling en goedkeuring van het manuscript.

Collegae

Alle collegae en met name de medepromovendi wil ik bedanken voor de gezellige tijd die ik bij de afdeling Klinische Farmacologie gehad heb. Vooral dank aan mijn kamergenoten Larissa en Heidrun. Larissa, met jou heb ik altijd heerlijk kunnen discussiëren over de epidemiologische aspecten van mijn onderzoek en ook heb ik veel goede herinneringen aan alle cursussen of congressen die we samen hebben bezocht (alhoewel jij ook wel eens alleen ging....). Ik ben blij dat jij mijn paranimf wil zijn! Enorm bedankt voor alles en succes met de afronding van jouw thesis. Heidrun, je was altijd behulpzaam, hoe druk je het ook had. Bedankt voor de gezellige tijd en veel succes met het afronden van jouw proefschrift en met je nieuwe baan in Tübingen. Ook de andere (oud)collega's van de Rationeel Geneesmiddelengebruik groep: Antje, Anuschka, Carel, Cornelis, Jaco, Jasperien, Liana, Lisa, Peter, Prashant, Willeke, en ook Amany en Mirjam, wil ik bedanken voor de gezellige momenten tijdens, maar zeker ook buiten het werk. Verder bedank ik ook de dames van het secretariaat Ellen, Alexandra en Ardy, en de beide heren Jan en Wessel voor jullie behulpzaamheid in de afgelopen jaren. Daarnaast wil ik ook Frank bedanken voor het ontwerpen van de omslag van dit proefschrift.
Verder wil ik ook de collega's van afdeling Sociale Farmacie en Pharmaco-epidemiologie bedanken voor jullie waardevolle feedback, vragen en adviezen tijdens onze dRugs-besprekingen en refereerbijeenkomsten.
Sinds een aantal maanden werk ik in het Juliuscentrum samen met prof dr A Algra en dr E Buskens aan een onderzoek om primaire preventie van beroerten te verbeteren. Nu mijn proefschrift af is, heeft dit project mijn onverdeelde aandacht. Ale en Erik, en mijn kamergenoten Erik en Iris, en alle andere Julianen, bedankt voor jullie steun bij de laatste loodjes van mijn proefschrift en voor de prettige samenwerking tot nu toe!

Vrienden

Mirjam & Michiel, Hetty, Carriene & André, Sofieke, Esther & Lars, Welmoed, Gert & Brenda, Annelies en niet te vergeten Gertrude wil ik heel hartelijk bedanken voor jullie gezelligheid, steun, leuke logeerpartijtjes, weekendjes weg en de filmavondjes. Carriene, jou wil ik in het bijzonder bedanken. Het is alweer meer dan vijf jaar geleden dat ik samen met jou mijn

onderzoeksstage in Zweden heb gedaan. Destijds ben ik enthousiast geraakt voor het doen van wetenschappelijk onderzoek. Dankjewel voor je vriendschap, interesse en je luisterend oor. Daarnaast blijven er een heel aantal mensen over die me een ontzettend leuke tijd in Groningen hebben gegeven. Heel erg bedankt!

Familie

Dan de basis van alles, mijn familie. Lieve papa en mama, bedankt voor alle liefde, hulp en steun die jullie al bijna 30 jaar geven. Ik kan jullie daarvoor nooit genoeg dankbaar zijn. En echt te gek pap dat je mijn presentatie op mijn allereerste internationale congres in Philadelphia kwam beluisteren! Lieve broers, zus, (bijna) schoonzussen en alle anderen dankjewel voor jullie liefde, hulp, steun en gebed. Ik ben blij jullie eindelijk het beloofde resultaat te kunnen laten zien. Lieve Egbert, ik vind het heel tof dat jij mijn paranimf wilt zijn! Daarnaast wil ik ook mijn lieve kleine neefjes bedanken, eindeloos kan ik van jullie genieten en even alles van mijn proefschrift vergeten. Bovenal dank aan mijn Vader in de hemel die zoveel om me geeft. Dank U voor uw liefde, genade en eindeloze trouw.

About the author

Jacoba Petronella Greving was born on March 15th 1977 in Groningen, the Netherlands. In 1995, after graduating secondary school at the Gomarus College in Groningen, she started her training in Nutrition and Dietetics at the Hanzehogeschool, Hogeschool van Groningen. In 1999 she obtained her Bachelor of Science degree and started her training in Nutrition and Health at the Wageningen University. As part of this training two research projects were conducted. The first project was at the Department of Human Nutrition and Epidemiology of the Wageningen University (supervisors: ir Anouk Geelen, dr ir Ingeborg A Brouwer and prof dr Evert Schouten), on validating a fish frequency questionnaire. The second project was at the Department of Medical Epidemiology of the Karolinska Institutet in Stockholm, Sweden (supervisors: dr Anna Bergström, prof dr Alicja Wolk and dr Pieter van 't Veer), on alcohol consumption and renal cell cancer. She obtained her Master of Science degree in Nutrition and Epidemiology in 2001.

In March 2002 she started the project described in this thesis at the Department of Clinical Pharmacology of the University Medical Center Groningen (supervisors dr Petra Denig, prof dr Flora M Haaijer-Ruskamp and prof dr Dick de Zeeuw). She joined the education program of the Groningen University Institute for Drug Exploration research school and was a member of the Evidence Based Medicine research group of the Northern Center for Health Care Research.

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Northern Center for Healthcare Research (NCH) and previous dissertations

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